Volume 17, Number 4

APRIL 1955

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Postgraduate Medicine

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Christopher's Minor Surgery — Edited by Ochsner & DeBakey

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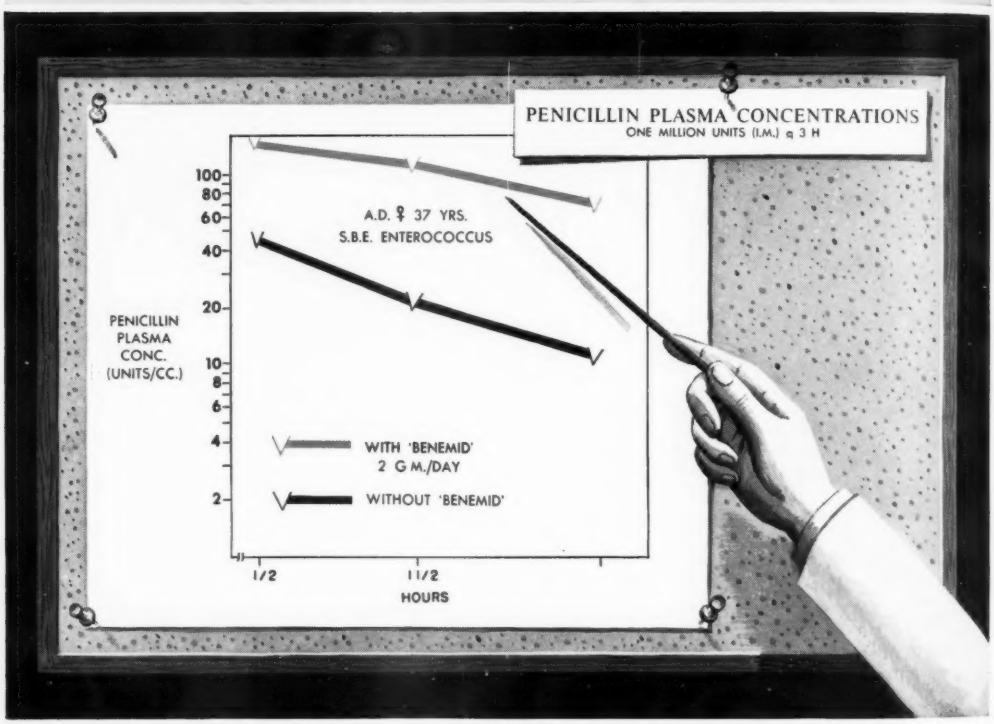

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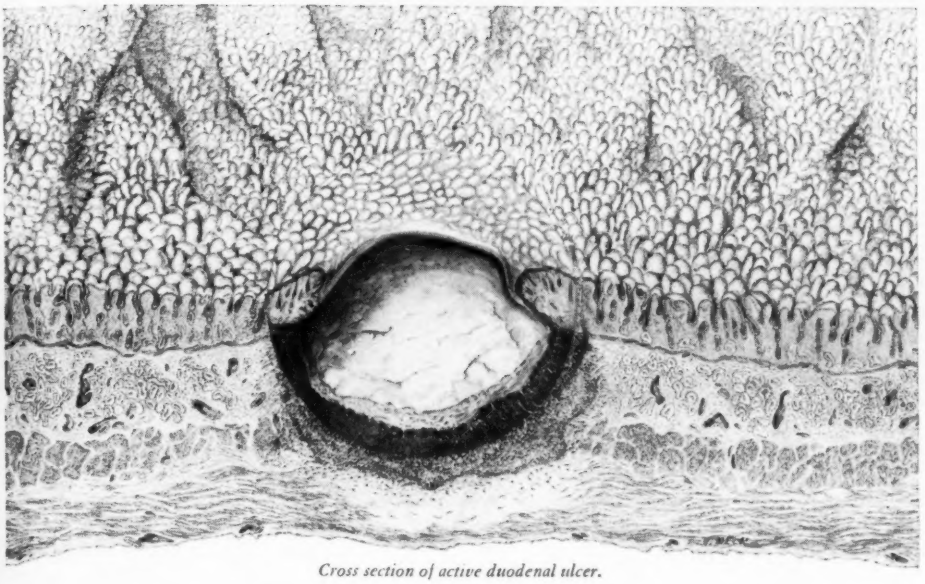

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

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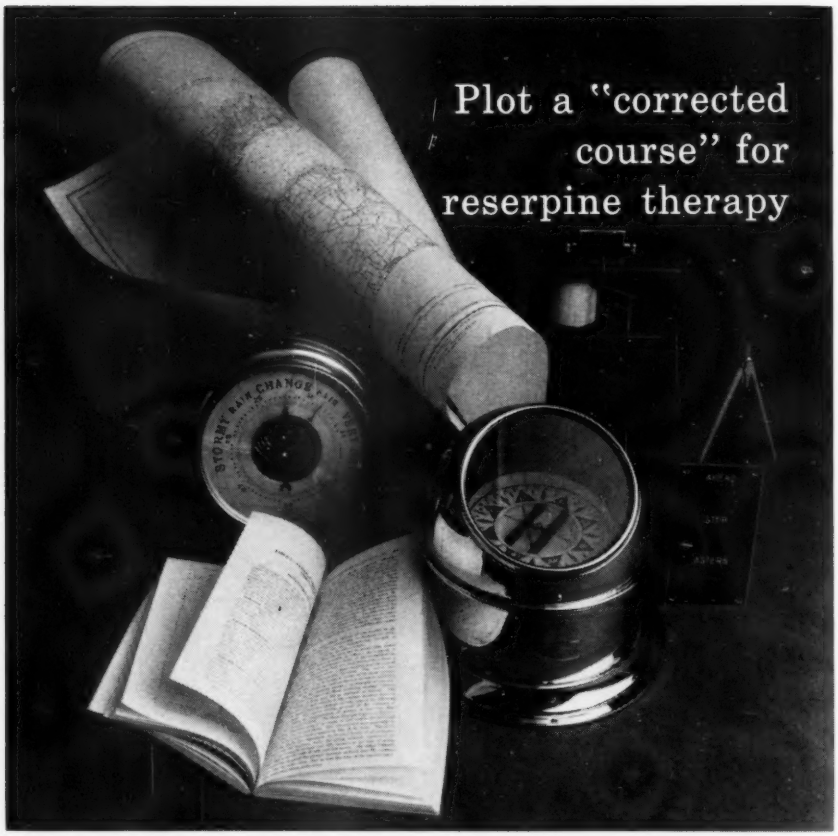

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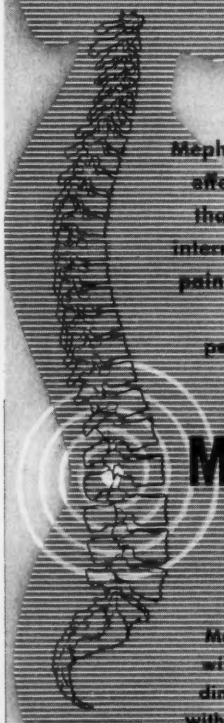

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1. Bender, T. J. Jr.: at Mtg. Med. Assoc. St. Alabama, Mobile, 1954.
2. Jessup, R., Murray, R. J. and Rossi, A.: Amer. Pract. & Dig. of Treatment, 5:792, 1954.

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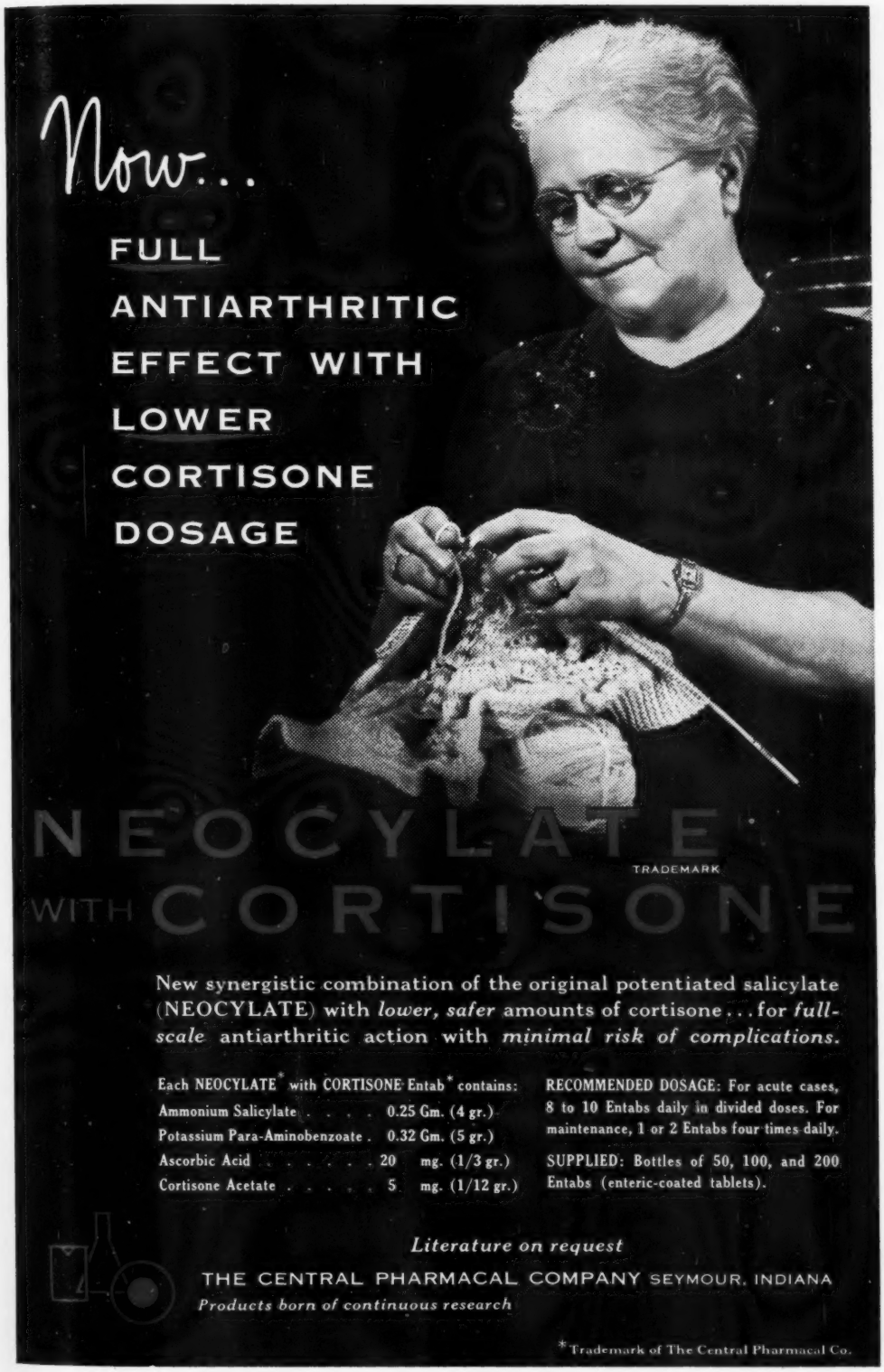

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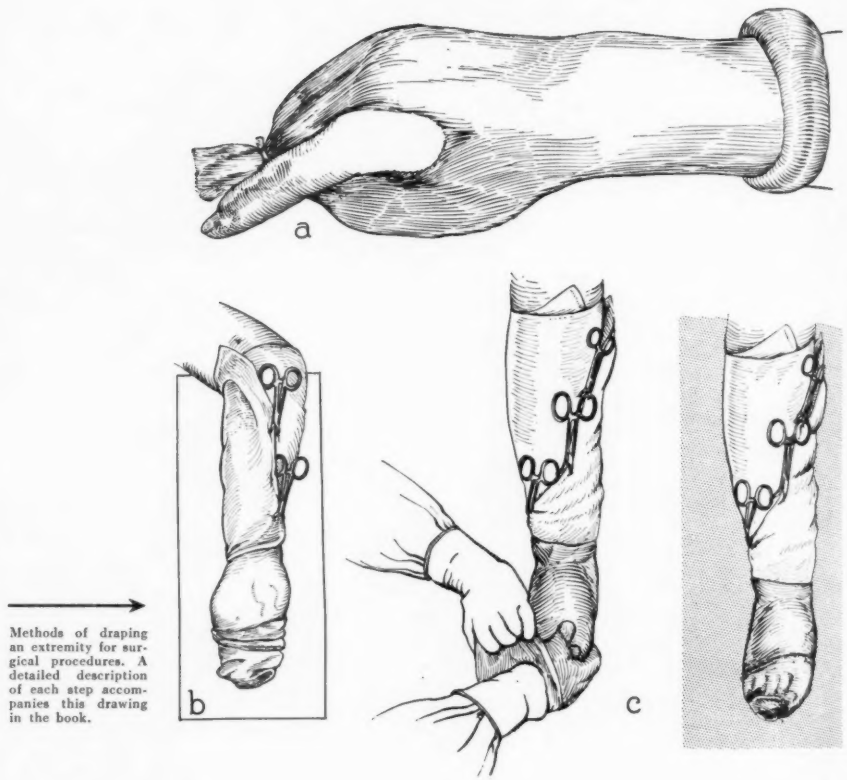

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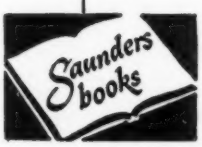

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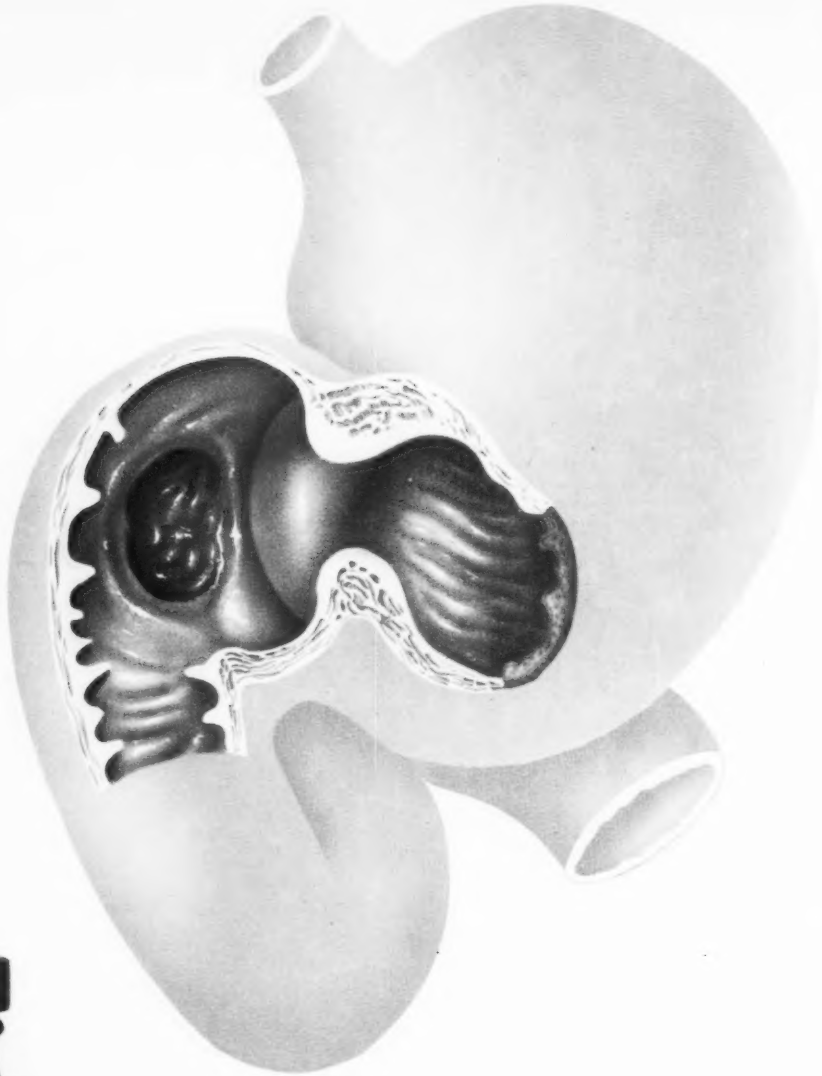

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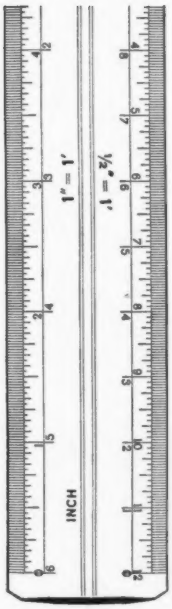

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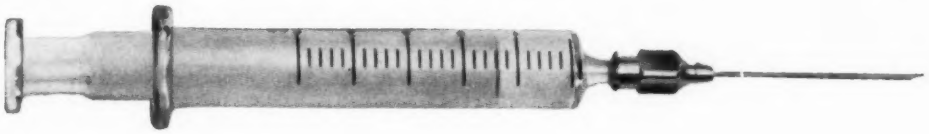
RIB-BACKS packaged in the *new* RACK-PACK eliminates unwrapping, handling or racking of individual blades. A real *time* and *labor* saver for the O.R. personnel. *In a matter of seconds* from RACK-PACK to sterilizer.

simplified emergency digitalization



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Parenteral: 'Wellcome'® brand Solution of Digoxin for Injection

in a vehicle of 40% Propylene Glycol and 10% Alcohol
0.5 mg. (0.25 mg. in each cc.) 2 cc. ampuls—Boxes of 12 and 100

dependable maintenance

Oral: 'Tabloid'® brand Digoxin

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Full information will be sent on request.

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• SLEEP

Q. A 43 year old businessman cannot get sufficient rest because of difficulty getting to sleep and staying asleep. For seven or eight years various drugs have been tried, including barbiturates and BENADRYL®, but these impair his efficiency almost as much as the lack of sleep. If he sleeps less than seven and one-half hours a night, his head aches, he is depressed and nervous and has no ambition. Many devices and methods have been employed to induce and maintain natural sleep, without success. However, the patient feels well for the rest of the day if he gets as little as two or three minutes of sleep during the day. What is the explanation for this change?

M.D.—Michigan

A. This patient's history is somewhat puzzling, probably because it is too brief for quick diagnosis. A complete and competent neurologic and psychiatric evaluation is indicated, preferably in a hospital. An electro-encephalogram, a spinal puncture, and roentgenograms of the skull might provide information as to whether the patient has a postencephalitic sleep disturbance or whether it is the result of a lesion of the hypothalamus. A battery of appropriate psychologic tests might point to a neurotic or psychotic depression, anxiety state, toxic confusional state (from barbiturates and other drugs), or even to an organic brain lesion. One or more psychiatric interviews certainly are indicated and probably would help greatly in making the diagnosis. I suspect that this patient has an anxiety state with depression, with superimposed symptoms of drug toxicity. Appropriate treatment will depend on the neurologic and psychiatric findings.

• DENTAL CARIES DURING PREGNANCY

Q. I am interested in the problem of preventing the dental deterioration which is so common during pregnancy. Can one assume that this is due to low blood calcium levels? During pregnancy, ACTH stimulation results, which probably leads to increased excretion of calcium and to low (?) blood calcium. If this is the cause of dental deterioration (and leg cramps), would daily HYTAKEROL® with calcium taken orally, with or without AMPHOJEL®, and reduced milk help this situation? Have any control studies been made, such as blood levels and clinical dental examinations, regarding this problem and the therapy suggested?

M.D.—Ontario

A. Because the physician observes the mouths of women during pregnancy and because many of those mouths show carious destruction of teeth, the myth that pregnancy causes dental caries persists.

Statistical studies of population groups by Mull, Bill and Kinney (Am. J. Obst. & Gynec. 27:679, 1954), Starobinsky (Deutsche Monatschr. f. Zahnh. 47:238, 1929) and Ziskin and Hotelling (J. Dent. Research 16:507, 1937) have shown that the decay rate does not increase during pregnancy. Shaw (J. Dent. Research 29:802, 1950) has confirmed this experimentally in rats. Mull, Bill and Kinney also showed that serum calcium and phosphorus levels were not related to caries, and Ziskin and Hotelling showed that the very slightly more acid mouths in pregnancy were not conducive to dental caries. Deakins and Looby (Am. J. Obst. & Gynec. 46:265, 1943)

(Continued on page A-22)

RAU-SED is preferable to barbiturates for sedation because it does not interfere with normal activity or alertness, provided dosage is properly adjusted.

RAU-SED

Squibb Reserpine

FOR SEDATION

0.5 mg. tablets, bottles of 50 and 500.
0.1 mg. and 0.25 mg. tablets, bottles of 100 and 1000.

SQUIBB

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demonstrated that the chemical composition of teeth is not altered in pregnancy; Klein (Dental Cosmos 77:864, 1929) experimentally showed that pregnancy does not cause caries; and Schour (J.A.M.A. 110:870, 1938), Robinson (J. Am. Dent. A. 30:357, 1943) and Burket (Oral Medicine. Philadelphia, J. B. Lippincott Company, 1946) explained the absence of a metabolic mechanism to permit withdrawal of calcium as a cariogenic factor.

Women should be taught the importance of oral hygiene (cleaning teeth after meals), of keeping concentrated carbohydrate consumption confined to regular and infrequent intervals and of brushing the gingivae during pregnancy as at other times. If calcium salts are to be prescribed they are not for the teeth of the mother or the fetus, which gets its tooth calcium even from osteomalacic mothers of India.

• TB CHEMOTHERAPY

Q. What, in your opinion, is the best chemotherapeutic program for treatment of a patient with minimal pulmonary tuberculosis, tuberculous pleurisy, tuberculous meningitis and tuberculous peritonitis? What is the value of ACTH, and what are the contraindications and hazards in its use? What other adjuncts to therapy do you suggest? The patient is an acutely and chronically ill 22 year old woman.

M.D.—Michigan

A. The three most frequently used drugs in treatment of tuberculosis are streptomycin, *p*-aminosalicylic acid (PAS) and isoniazid. For persons who are allergic to one or more of these drugs, or in cases in which tubercle bacilli have become resistant to one or more of them, neomycin may be used.

For adults with pulmonary tuberculosis, two of the drugs should be given simultaneously, e.g., streptomycin and isoniazid, or streptomycin and *p*-aminosalicylic acid. A combination of two drugs is more effective than either one alone. The usual dosages for adults are: 1 gm. of streptomycin intramuscularly every three days; 12 gm. of PAS orally in four equal doses daily; 4 to 8 mg. of isoniazid per kilogram of body weight orally in three equal doses daily.

All three drugs may be administered simultaneously in the above dosages in cases of such

(Continued on page A-24)

osteoporosis causes bone to become fragile, less elastic, and more susceptible to fractures *

*Steindler, A., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 693.

"PREMARIN" with METHYLTESTOSTERONE

Ideal preparation for combined estrogen-androgen therapy

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In this... "the Commonest Disease of Civilized Man"

● In hypertension, management can now be started in the earliest stages ... to retard progression, with the goal of prolonging useful life.

● Fully one half of all cases of mild, labile hypertension can be controlled with simple Rauwiloid therapy.

● Rauwiloid accomplishes what mere sedation cannot . . . the patient is spared the reaction to tension situations . . . without somnolence, without clouded sensorium, without change in alertness.

● The feeling of well-being engendered by Rauwiloid may become manifest as soon as 24 to 48 hours after the first dose. Its antihypertensive effect becomes apparent in two to three weeks.

● In the face of tension-producing stimuli, Rauwiloid, through its sedative and bradycrotic properties, provides tranquil equanimity.

● Its dosage schedule is uncomplicated, definite, easy to follow: Merely 2 tablets at bedtime. For maintenance, 1 tablet usually suffices. No contraindications.

Rauwiloid® *First Thought IN HYPERTENSION*

Riker LABORATORIES, INC., LOS ANGELES 48, CALIF.

serious and often fatal forms of tuberculosis as meningitis and miliary disease; streptomycin is then given daily for 10 days or two weeks and then every three days. Isoniazid apparently is the most effective drug in treating meningitis.

Use of ACTH and cortisone in tuberculosis is still highly controversial. There are those who believe they worsen tuberculous lesions, whereas others feel they do not have a deleterious effect and occasionally may be helpful. Until more evidence is available, these agents probably should not be used in treating tuberculosis.

• DIGITALIZATION BEFORE SURGERY

Q. A question has arisen several times in the past year at our hospital regarding the advisability of prophylactic digitalization of elderly patients prior to their having major surgery. We find no mention in the textbooks of such a procedure. On several occasions during this past year we have had the opportunity to raise the question that I put before you. We have in mind particularly those cases of people over the age of 80 who come into the hospital in a debilitated state with such a condition as bowel obstruction with severe toxemias. The question has usually come up postoperatively when the need for digitalis has become evident.

We question whether these patients would fare better had they been digitalized prior to surgery.

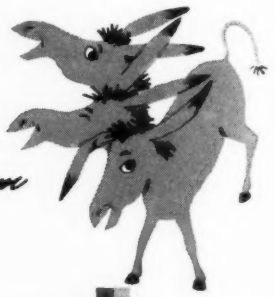
M.D.—Missouri

A. Routine prophylactic digitalization of elderly patients prior to major surgical operations is contraindicated. When patients have cardiac disease to such a degree that congestive failure, auricular flutter or auricular fibrillation might occur postoperatively, the evidence in favor of digitalization usually can be determined before operation by evaluation from the cardiac standpoint.

On the other hand, the reader mentions, the condition of patients coming into the hospital for emergency operations may be difficult to evaluate from this standpoint, but even in this situation, *routine* prophylactic administration of digitalis is not indicated. One of the reasons for this is that when digitalization is needed, it can be carried out postoperatively with only a brief delay by means of the parenteral administration of a preparation such as lanatoside C (CEDILANID®).

up against this stubborn trio?

nervous tension
associated pain
smooth muscle spasm



IMPLEMENT YOUR TREATMENT WITH EFFECTIVE buta

BY THE CONCERTED ACTION of the natural alkaloids of belladonna and the mild, antispasmodic effect of CLORTRAN, BUTADONNA provides at once spasmolysis, sedation and a local anesthetic effect on the gastrointestinal mucosa. The belladonna alkaloids, asserts W. T. Salter, "have withstood the 'acid test' of medical experience over the centuries." Combined with these in management of hypermotility and spasm, an exceptionally rational choice is CLORTRAN — non-barbiturate sedative without side effects, which allays excitement centrally and eases pain peripherally.*

**Textbook of Pharmacology, (Saunders) 1952.*

Wampole LABORATORIES

There is no question that the patients mentioned by the reader would have fared better had they been digitalized prior to operation.

• XANTHOMA DISSEMINATUM

Q. I would appreciate some information about the most recent treatment of xanthoma disseminatum if drugs exist to cure this disease. My patient is eight years old and there are many cases of xanthelasma in his relatives. Blood cholesterol is a little increased.

M.D.—Quebec

A. If the disease in question actually is xanthoma disseminatum, there is no satisfactory treatment. However, if the disease is xanthoma tuberosum, which the familial history and elevated values for cholesterol would indicate might be the situation, there are treatments that may be tried. None is completely satisfactory.

Xanthoma disseminatum involves chiefly the flexural and intertriginous areas, buccal membrane and tongue, may involve the nasopharynx and larynx, and be associated with diabetes insipidus. Values for lipids are normal.

Xanthoma tuberosum involves predominantly the extensor surfaces of knees and elbows; there may be associated xanthelasma and xanthomas of tendon sheaths. Values for lipids are consistently elevated.

Recent trends in the treatment of tuberous xanthomatosis include the administration of choline derivatives and heparin and prescription of a diet low in both animal and vegetable fat (not to exceed a daily intake of 30 gr.). The administration of heparin is potentially dangerous. The diet is unpalatable and the majority of patients refuse to follow it for the length of time required to produce beneficial results—a matter of months. The administration of choline preparations has not proved worthwhile with most investigators. Those lesions that are painful, easily traumatized or interfere with motion may be excised.

• HYPERVENTILATION TETANY

Q. Is there any explanation for the mechanism of pain described as numbness (not hypesthesia) associated with severe nervous tension? There

(Continued on page A-26)

INDICATIONS: hypertonic and spastic states of gastrointestinal, genitourinary and biliary tracts, especially when nervous tension is present. Also in dysmenorrhea, functional nausea, vomiting and motion sickness.

EACH ***BUTADONNA*** *CAPSULE CONTAINS:*

Clortran (Chlorobutanol) .....0.25 gm. (3-3/4 gr.)
Hyoscyamine Sulfate .....0.1 mg.
Atropine Sulfate .....0.02 mg.
Hyoscine Hydrobromide ..... 0.007 mg.
Total Alkaloidal salts ..... 0.127 mg. (1/500 gr.)

donna

NEW SPASMOLYTIC-SEDATIVE

DOSAGE: One capsule three times a day, half hour before meals. As a night time spasmolytic-sedative, two or more capsules at bedtime.
SUPPLIED: Bottles of 100.

Sedative-Hypnotic-Antinauseant
clortran
free of
• residual symptoms of the barbiturates,
• gastric irritation caused by other chloral derivatives

samples and literature on request!
Henry K. Wampole & Company, Inc. • 440 Fairmount Ave., Philadelphia 23, Pa.

are no positive evidences of intrinsic neurologic, vascular or musculoskeletal disease in the arms. This symptom is always present during the time of the patient's major manifestations of nervous tension, which are nausea, anorexia and dysentery. It is never present when these symptoms are absent. The patient is aware of the psychogenic origin of his symptoms.

M.D.—Kansas

A. Numbness of the hands is the first sign of hyperventilation tetany. It can be produced by having the patient overbreathe vigorously for a minute, and it can be abolished by holding the breath for a minute or by running around the block. When the numbness is quite marked, a positive Chvostek phenomenon should be found.

The mechanism is probably peripheral since hyperventilation alkalosis produces constriction of the peripheral arterioles. It has been shown, however, that hyperventilation also can reduce cerebral blood flow as much as 50 per cent.

• PUSTULAR PSORIASIS

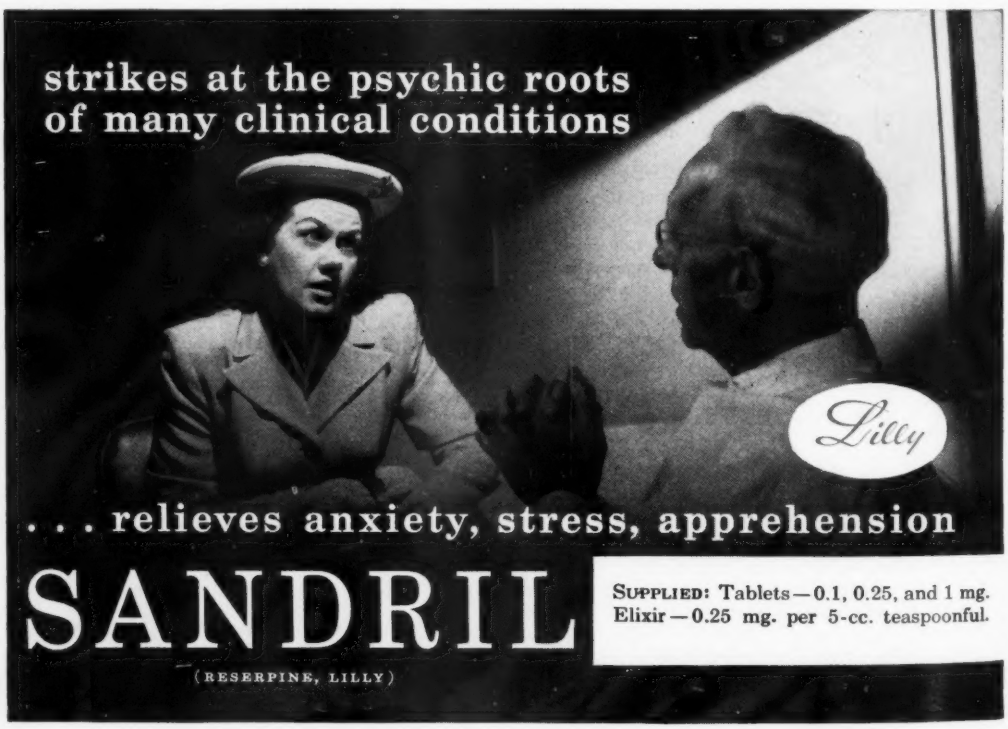
Q. A 45 year old woman has an itchy, scaly, pustular erythema on the palms of both hands and involving the nails, which are deformed and raised from the nail bed at the distal parts. The condition began about three years ago on the right palm and about 18 months ago on the left hand. The patient thinks she had a milder form of the condition when she was in high school and again when she was teaching school. It cleared up spontaneously. This time it is persistent and has not responded to any treatment. She has had local applications, x-ray treatment, quartz lamp treatment, crude tar ointment and also vitamin injections.

My own diagnosis is psoriasis and my only treatment has been with a quartz lamp and tar, which I think has effected some improvement, but the skin is still thickened. What is the diagnosis, prognosis and treatment suggested?

M.D.—Ontario

A. The description sounds like a pustular psoriasis. I would suggest first chloroquine, 0.25 gm. tablets twice daily orally, and VIOFORM® ointment locally.

If there is no improvement, switch to pregnenolone acetate tablets, 100 mg. twice daily, and BISTRIMATE® (oral bismuth), 2 tablets three times daily.



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Mephyton®

(VITAMIN K_1, MERCK)

Preferred product for routinely stabilizing prothrombin levels before surgery

MAJOR ADVANTAGES: Action detectable within 15 minutes; complete reversal of hypoprothrombinemia within 4-12 hours.

There are three significant reasons for preferring MEPHYTON over the menadione derivatives. The action of MEPHYTON is: (1) more rapid, (2) more complete, and (3) more prolonged. These advantages apply to either simple vitamin K deficiency states or in anticoagulant-induced hypoprothrombinemia. In the latter condition, MEPHYTON provides the *most* dependable and practical means of restoring normal levels of prothrombin.

INDICATIONS: Hypoprothrombinemia due to Dicumarol®, Cumopyran®, Hedulin®, Tromexan®, antibiotics, salicylates, obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, and deficiency of vitamin K in the newborn.

SUPPLIED: In boxes of six 1-cc. ampuls, each cc. containing 50 mg. of vitamin K_1.

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For many years clinicians and surgeons have recognized the therapeutic value of the high protein dietary.

In more than normal amounts, protein is essential in the treatment of many diseases characterized by hypoproteinemia[1]—nephrosis,[2] sprue, pellagra, chronic colitis, certain liver afflictions,[3] anorexia of diverse etiologies. High protein intake helps to stabilize tissue protein in diseases in which protein catabolism is increased, such as hyperthyroidism and protracted high fever. Dietaries high in protein promote wound healing in the surgical patient and speed convalescence.[4] Sufficient protein ingestion constitutes a protective measure in the geriatric patient.[5] Large amounts of protein are required to satisfy the growth and other metabolic needs of the pediatric patient.

Meat provides large quantities of protein highly effective in the body economy—tissue growth and maintenance, formation of antibodies, enzymes, and protein hormones, and regulation of fluid balance. It also supplies valuable amounts of B vitamins and essential minerals including iron, phosphorus, and potassium. Appeal to the palate, easy digestibility, and its nutrient contribution make meat an important component of therapeutic diets.

---

1. Taggart, H. A.: Protein Metabolism in Relation to Nutritional Aspects of Medical Diseases, Pennsylvania M.J. *54*:339 (1951).
2. Marquardt, G. H.; Cummins, G. M., and Fisher, C. I.: Blood Protein Replenishment in Treatment of Nephritic Edema, Quart. Bull. Northwestern Univ. M. School *26*:140 (1952).
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4. Kekwick, A.: Protein Deficiency in Surgical Patients, Ann. Roy. Coll. Surgeons England *7*:390 (1950).
5. Stieglitz, E. J.: Nutrition Problems of Geriatric Medicine, Report of Council on Foods and Nutrition, J.A.M.A. *142*:1070 (Apr. 8) 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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Diamox*

ACETAZOLEAMIDE LEDERLE

NOW ACCEPTED FOR USE IN

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Recent clinical trials show that DIAMOX suppresses both the frequency and severity of epileptic seizures. DIAMOX appears to produce a relative acidosis, in a manner similar to the ketogenic diet, and may also have a direct effect on nerve tissue. No direct sedative action is apparent.

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Oral administration of DIAMOX is followed by significant reduction in intraocular pressure in acute glaucoma. Experimental evidence indicates decreased secretion of aqueous humor. DIAMOX also appears to enhance the action of commonly employed miotics.

CARDIAC EDEMA

Now the most widely prescribed drug of its type, DIAMOX has been immediately accepted by clinicians because it is an effective, safe and convenient *oral* diuretic.

Available in 250 mg. tablets and 500 mg. ampuls for intravenous use.

1. MERLIS, S.: Diamox: A Carbonic Anhydrase Inhibitor—Its Use in Epilepsy. Neurology. 4:11, 863-866 November 1954.

2. BECKER, B.: Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, Diamox. Am. J. Ophth. 37:1, 13-15 January 1954.

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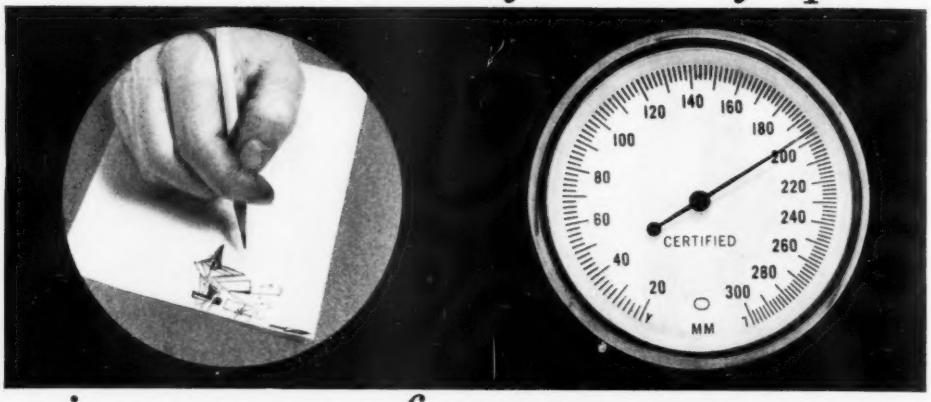
Emotional tension is just one symptom



...in most cases of HYPERTENSION

keep the
blood pressure
down longer . . .
and the patient
calm . . . with

Veralba/R*

PROTOVERATRINES A AND B WITH RESERPINE

In mild, moderate, and severe hypertension, VERALBA/R usually maintains blood pressure at approximately normal levels indefinitely. It offers "combined" drug therapy that is both safe *and* effective. Establishing precise dosage is a simple process with VERALBA/R, and side effects are usually insignificant.

Supplied in bottles of 100 and 1,000 scored tablets, each containing 0.4 mg. of protoveratrines and 0.08 mg. of reserpine.

*TRADEMARK

Standardized with mathematical accuracy . . . by chemical assay

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PREOPERATIVE SEDATION...

one of the 44 uses for

short-acting **NEMBUTAL®**

(Pentobarbital, Abbott)

Just 0.1 Gm. (1½ grs.) of short-acting NEMBUTAL the night before and 0.1 to 0.2 Gm. (1½ to 3 grs.) two hours before operation will allay apprehension, induce sleep and decrease the amount of general anesthetic needed. And with these advantages:

➡ *Short-acting* NEMBUTAL *can produce any desired degree of cerebral depression—from mild sedation to deep hypnosis.*

➡ *The dosage required is small—only about one-half that of many other barbiturates.*

➡ *Hence, there's less drug to be inactivated, shorter duration of effect, wide margin of safety and little tendency toward morning-after hangover.*

➡ *In equal oral doses, no other barbiturate combines quicker, briefer, more profound effect.* Abbott

a Brighter Prognosis for your

HERPES ZOSTER PATIENTS

when you use

PROTAMIDE®

(Sherman)

because published studies* show:

"Good to excellent results" in more than 80%, with "almost immediate improvement."

Prompt recovery in more than 90% when Protamide is started in the first week of symptoms.

Why not use Protamide first?

. . . for herpes zoster, post-infection neuritis, chickenpox, and other nerve root pain such as tabes dorsalis.

A sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.

CLINICAL DATA ON REQUEST

*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

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What's Happening in medicine

APRIL 1955

POSTGRADUATE MEDICINE'S report
of late news of interest to the
practicing physician

ATOMIC BOMB AND DRUGS

Biologicals within 1000 yards of an atomic explosion will be safe for use if their containers are not damaged, the U.S. Food and Drug Administration reports.

Forty-two common drug preparations were exposed to tests in Nevada in 1953. Among them were blood extenders, morphine, aspirin, nitroglycerin and digitalis, sulfonamides, antibiotics, cortisone, phenobarbital and vitamin tablets. Only insulin and vitamin B_{12} showed a reduction in potency, about 10 per cent and 50 per cent, respectively.

DRYING THE "RUNNING" NOSE

Use of hydrocortisone spray to stop continuous sniffles and to dry dripping noses of hay fever sufferers is reported by Drs. John H. Burger and Joseph H. Shaffer of Henry Ford Hospital, Detroit.

The doctors told a New York Academy of Sciences conference that no side reactions occurred. The hormone was not absorbed into the blood stream through the membranes of the nose. When the drug is stopped, however, symptoms return in a week or two.

Comparing the effects of hydrocortisone with those of its predecessor, cortisone, Dr. John C. Laidlaw, University of Toronto, reported hydrocortisone given by mouth or injected into inflamed joints of arthritis and bursitis patients is more potent.

Dr. Laurance Kinsell of Oakland, Calif., pointed up the value of combined use of hormones and antibiotics in overwhelming infections. The hormones can eliminate the fatal toxic effects of infections until the antibiotics have had time to destroy the germs.

Dr. Joseph B. Kirsner, University of Chicago, said 33 of 40 patients with ulcerative colitis had benefited through oral treatment with hydrocortisone.

CORTISONE FOR STROKES

Cortisone is helpful in the immediate therapy of apoplectic stroke, Dr. Henry I. Russek of New York City reported to the American Geriatrics Society. He said 21 of 35 patients showed good response within 24 hours. They were converted from discouragement and apathy to alertness and even euphoria. Aside from the improvement in the emotional state, paralytic signs are also improved, Dr. Russek said. There is less incoherence and aphasia. With subjective improvement afforded by cortisone therapy, rehabilitation can be started within 48 hours, making possible early neurologic recovery.

Questions mass x-rays for cancer

The three year survival rate of lung cancer detected by population surveys is 12 per cent, or about the same as that detected under normal conditions of practice, contends Dr. L. H. Garland, San Francisco radiologist.

Surveys may actually decrease the number of cancer cures because of the false sense of security developed by persons who are reported to have a negative minifilm, he told the Lane Medical Society (California).

Dr. Garland believes about half of the "positives" are being missed in surveys. The detection rate is only 10 per 100,000 and the known prevalence rate is 20 per 100,000.

Dr. Garland stresses the need for a better means than the photofluorogram for detecting curable lung cancer. He suggests studies on serologic tests and sputum cytology.

Nylon "no kink" artery

Prefabricated artery replacements of nylon for permanent bridging of arterial defects have been developed by the Chemstrand Corporation of Decatur, Ala. Successful use on the first patient has been reported to the Society of University Surgeons by Dr. W. Sterling Edwards of the Medical College of Alabama. A femoral artery was restored in a middle-aged man. He showed normal circulation in his foot one month later.

While fabric tubes have been used in the last two years, they have been handmade. The new technic makes the textile arteries available on a large scale through machine production. Dr. Edwards said the arteries maintain flexibility but will not kink. They are easily applied by the surgeon.

Cabbages and kings

A combination of two vitamin substances found in many foods, including cabbage, is capable of strengthening the capillaries. The chemicals are called bioflavonoids.

Dr. Alfred Szent-Györgi, discoverer of the substance named vitamin P, told a New York conference that mankind's capillaries may well be a key to a major understanding of the entire process of life.

"There is no real difference between cabbages and kings," he said. "If the king's capillaries do not work well, and you can put them right again by an extract of cabbage, then this means that you have set one precision mechanism right by taking out an identical screw from another, similar precision mechanism. The good fit only shows the close relation, the essential identity of the two systems."

Dr. Charles E. Brambel of Mercy Hospital, Boston, said the bioflavonoids prevented capillary bleeding in patients receiving anticoagulant therapy for coronary disease.

Golf hands

Gripping golf club handles too tightly, too often and without sufficient interruption can produce swollen, painful, tender hands, points out Dr. Philip Lewin of Chicago. The condition occurs chiefly in women after the midseason of golf and is most common in those who are going through or have completed the menopause.

As treatment, Dr. Lewin seeks to increase the thickness of the golf club handles with rubber wrappings. Unfinished calf gloves are recommended, as the ordinary gloves are too thin. They may be removed for short approach shots and putting. The patient is also instructed to interrupt the golf schedule for one week and to limit subsequent play.

G

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Single Tablet Combination Therapy in Hypertension

GREATER EFFICACY FROM SMALLER DOSAGE

SIDE ACTIONS FEWER AND OF LESSENED INTENSITY

NO COMPLICATED DOSAGE SCHEDULES

SIMPLER PATIENT MANAGEMENT

RAUWILOID® + VERILOID

Indicated in moderately severe hypertension and in cases not responding to Rauwolfia alone. The combination containing Rauwiloid 1 mg. and Veriloid 3 mg. permits better tolerated doses of Veriloid to exert full hypotensive effect and leads to rapid symptomatic relief, while the contained Rauwiloid provides a tranquil sense of well-being. Initial dose, 1 tablet t.i.d., p.c. In bottles of 100.

RAUWILOID® + HEXAMETHONIUM

When ganglionic blockade is called for in rapidly progressing, otherwise intractable hypertension, Rauwiloid + Hexamethonium (each tablet containing 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate) serves with greater efficacy and greater safety. The combination provides smoother, less erratic response to hexamethonium and permits greatly reduced dosage of the latter drug (up to 50% less). Initial dose, ½ tablet q.i.d. In bottles of 100.

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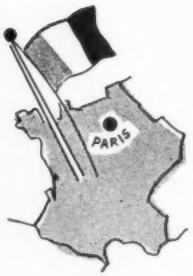
FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

PARIS



Artificial hibernation in pediatrics—Artificial hibernation is induced by means of neuroplegic drugs and by refrigeration. The over-all effect is a calming of the disorganized reactions of the neuro-endocrine system, such as result from trauma and severe infections. The method is applicable to infants born at term, but not as yet to prematures. The neuroplegic drugs favored in France are LARGACTIL® (chlorpromazine hydrochloride) which potentiates phenobarbital, the antihistamines, PHENERGAN® and phenobarbital. Refrigeration or cooling is effected either by transferring the patient to a room kept at a temperature of 17° C., or by placing ice packs on the head and over blood vessels. The body temperature desired is 36° C.

Use of artificial hibernation may be lifesaving in surgical as well as medical cases; that is, wherever it is necessary to eliminate dangerous antistress reactions (especially states of shock). More generally, indications for artificial hibernation are: disorders of the neurovegetative system, convulsions, chorea, meningeal encephalitis, tetanus; respiratory difficulties and serious pneumonopathies; circulatory disorders (hyperthermia, collapse, toxicosis); digestive disturbances (choleraic diarrhea), and metabolic disorders (e.g., hyperthyreosis). Refrigeration is not applied to infants for minor disorders, such as diarrhea of neurologic origin, vomiting due to pyloric stenosis or pyloric spasm, and enteritis; Largactil and phenobarbital only are used.

Artificial hibernation is an exacting procedure which requires hospitalization and competent doctors and nurses. A combination of Largactil and Phenergan, mixed in equal amounts, may be administered by intravenous drip (usually for serious and urgent cases), or by the intramuscular or subcutaneous route. Phenobarbital must be given separately (0.01 gm. per kilogram of body weight daily). The dosage of each of the two drugs of the Largactil-Phenergan combination is 1.5 mg. per kilogram daily for infants less than one month old, 2 mg. per kilogram daily for infants up to 12 months old, and 2 to 4 mg. per kilogram for those from one to five years old. In mild cases, drops of the neuroplegic drugs may be placed under the tongue for slow absorption. Largactil and Phenergan are usually administered intramuscularly; the injections must be repeated, however, at two hour intervals because of the rapid dissipation of the action of Largactil. Use of the subcutaneous route necessitates continuous perfusion and the addition of hyaluronidase (10 units per 125 units of the Largactil-Phenergan mixture).

Artificial hibernation is initiated by first injecting an intramuscular dose of phenobarbital and then one-third of the total daily dosage of the "lytic cocktail" mixture of Largactil and Phenergan. A significant thermolytic drop is obtained in three to six hours; the drop is still further increased and then maintained by giving the rest of the daily "cocktail" dosage by the intravenous, intramuscular or the subcutaneous route. The action of these neuroplegic drugs is supplemented by refrigeration, as has already been indicated. Oxygen therapy is not required unless anoxia develops.

Some of the more overt effects of artificial hibernation which can serve as criteria of its action are the calm and relaxed appearance of the patient, facial pallor, slowed pulse and nor-

(Continued on page A-36)

Upjohn

Gradual and sustained lowering of blood pressure:

Reserpoid

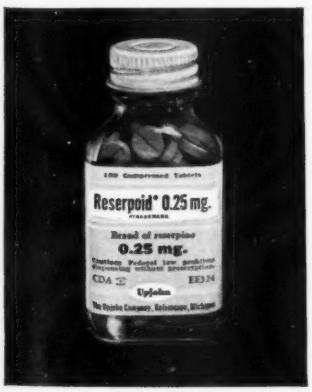
TRADEMARK FOR THE UPJOHN BRAND OF RESERPINE

(Pure crystalline alkaloid)

Each tablet contains:
Reserpine ..... 0.1 mg.
or 0.25 mg.
or 1.0 mg.

Supplied:
Scored tablets
0.1 and 0.25 mg. in bottles of 100 and 500
1.0 mg. in bottles of 100

The Upjohn Company, Kalamazoo, Michigan



mal or slightly lowered arterial pressure, and regular and forceful respiration. As stated before, the body temperature should be held stable at about 36° C. The average duration of the state of hibernation is from 24 to 36 hours, with extremes of 10 and 72 hours. It is terminated by first removing the ice packs and then stopping the injections. The normal temperature is regained in one to three days.

Untoward reactions are rare. Among those that may occur is bronchorrhea caused by an overdose of Phenergan, which would necessitate either discontinuing the drug or correcting the dosage. The possible occurrence of secondary hemorrhages can be avoided by giving vitamin P (10 mg. per day) and vitamin K (25 mg. per day). Paralytic ileus can similarly be prevented by administering PROSTIGMIN® (0.4 mg. per kilogram of body weight daily). Finally, denutrition and eschars can be treated by the use of DOCA® and androgens.

Late complications of neurosyphilis—The account which follows summarizes the high points of the extremely important discussion which followed the report on a patient formerly afflicted with syphilis and general paresis, made by Dr. Boudin last December at the meeting of the French Society of Dermato-Venereology. Two courses of malariotherapy stopped the general paresis, steadied the mental disorientation of the patient, and made it possible for him to perform light and easy tasks. His serologic tests and Nelson test became negative. However, during the last two years arthropathies of the tabetic type developed in the knees and the spinal column and are slowly progressing.

The discussion was concerned with the following points: (1) serologic reactions, (2) diagnosis, (3) the real origin of the arthropathies, and (4) therapy. Negative serologic reactions are no longer considered decisive evidence of a syphilis cure. This is not true, however, of the Nelson test, for it remains decisively positive irrespective of the subsequent evolution or arrest of the old syphilitic infection. Durel has noted that this test may occasionally become spontaneously negative in some cases. On the other hand, in his study of some 200 cases of tabes, Boudin encountered only one negative Nelson test of this nature. From a practical standpoint, a positive Nelson test must therefore be considered valid evidence of infection.

(Continued on page A-38)

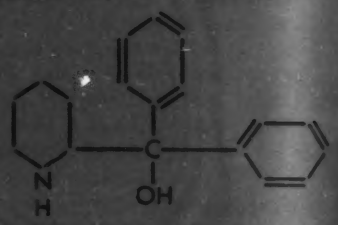
Rx INFORMATION

Meratran

Actions: Meratran is an entirely new and different central motivant that acts on the subcortical area of the brain. This portion of the brain is thought to expedite or facilitate intellectual activity which originates in the cortex. Meratran, when administered to the emotionally tired and depressed patient, subtly restores him to his usual level of alertness, interest and productivity.[4,5]

Indications: Emotional fatigue, unhappiness of more common type (financial worry, social stress). Situational stress or *mild* depression. Adjunctive therapy in certain psychoses and psychoneuroses.[6,7]

Composition: alpha-(2-piperidyl) benzhydrol hydrochloride with the following structure:



Dosage: For emotional fatigue and mild depression, *1 to 6 mg. daily. Individual patient response must be observed and daily dosage and duration of administration adjusted to patient response.*

Supplied: Small pink tablets containing: 1 mg. Meratran (pipradrol) hydrochloride.* Bottles of 100.

1. Brown, B. B. and Werner, H. W.: Pharmacologic Studies on a New Type of Central Stimulant, Federation Proc. 12:304, 1953. 2. Brown, B. B. and Werner, H. W.: Pharmacologic studies on a new central stimulant, alpha-(2-piperidyl) benzhydrol hydrochloride, J. Pharm. and Exp. Ther. 110:180, 1954. 3. Blohm, T. R., et al.: Tissue distribution and excretion of alpha-(2-piperidyl) benzhydrol hydrochloride, Federation Proc. 13:337, 1954. 4. Heath, R. C.: Discussion of paper by Howard D. Fabing (alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant in the treatment of blepharospasm, spasmodic torticollis and narcolepsy) presented before the American Neurological Association, Atlantic City, June 14, 1954. 5. Fabing, H. D., Hawkins, J. R., Moulton, J. A. L.: Clinical studies on alpha-(2-piperidyl) benzhydrol hydrochloride, a new antidepressant drug. Presented before the American Psychiatric Association, St. Louis, Missouri, May 3, 1954. 6. Fabing, H. D.: Alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant, in the treatment of blepharospasm, spasmodic torticollis and narcolepsy; preliminary report (Motion Picture Demonstration), American Neurological Association, June 14, 1954. 7. Hiswich, H. E.: Discussion of paper (reference 2), American Psychiatric Association, May 3, 1954.
*Alpha-(2-piperidyl) benzhydrol hydrochloride.

The Wm. S. Merrell Company
CINCINNATI
New York • St. Thomas, Ontario
PIONEER IN MEDICINE FOR OVER 125 YEARS

T. M. MERATRAN

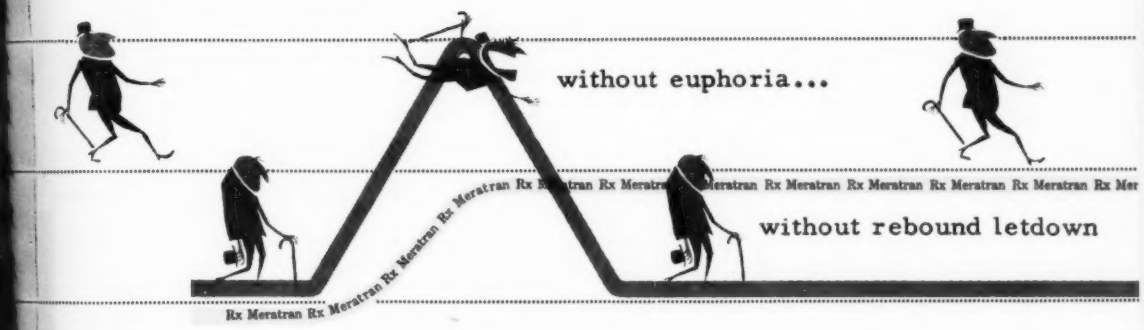
NEW DRUG

Meratran

(pipradrol hydrochloride)

a unique central motivant for the treatment of the emotionally tired and depressed patient

subtly returns your emotionally fatigued and depressed patients to their usual level of alertness, interest and productivity...


without euphoria...
without rebound letdown
Rx Meratran Rx Meratran Rx Meratran

In the case under discussion, it is established that the patient formerly had syphilis. But the question as to the syphilitic nature of the progressing arthropathies must remain contentious, especially in the presence of the negative Nelson test. However, the articular damage and dislocations are undoubtedly similar to those encountered with neurosyphilis. A case is recalled in this connection in which Adie's syndrome was mistaken for the Argyll Robertson sign. But on the evidence of a negative Nelson test the neurologist would not admit a diagnosis of neurosyphilis, and instead sent the patient to an ophthalmologist who correctly established the presence of Adie's syndrome.

Could it be that the arthropathies are evidence of an evolving syphilitic infection? Here it is recalled that in France, some 30 years ago, Gougerot and Sezary emphasized the two following pathogenic possibilities: (1) neuropathies directly related to syphilitic evolvement and responsive to its treatment, and (2) damages deriving from an evolving bulbar sclerosis which progresses spontaneously in spite of the elimination of syphilis. The symptoms in both cases are identical; they show the same arthropathies and the same old tabetic series of symptoms; the serologic reactions are either negative or indifferently positive and unresponsive to treatment. To this may now be added the Nelson test which, when positive, affords proof that syphilis has been present. It therefore is impossible to establish a diagnosis based on clinical evidence alone.

Recourse to "trial treatment" is the only available means to resolve the question of diagnosis. It is recalled that Gougerot long ago emphasized his successful treatment with intramuscular calomel of patients with active syphilis, as contrasted with the very poor tolerance to the drug displayed by patients freed from this infection. In patients with progressive sclerosis not due to *Treponema*, the treatment caused such aggravation of pain that it had to be stopped. Today, treatment should first be tried with penicillin. It must be applied with extreme caution and stopped if the neurologic symptoms worsen.

It is concluded that in spite of progress made in serologic and therapeutic methods, the problem of the late complications of neurosyphilis remains as it was 30 years ago. We still cannot give a precise answer to the question of whether or not the progressive neurologic lesions which are present in a patient who formerly had syphilis are caused by the *Treponema* infection.

Lederle

FOLBESYN*

Vitamins *Lederle*

A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and B_{12}) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

Dosage: 2 cc. daily. Each 2 cc. provides:

Thiamine HCl (B_1)	10 mg.
Sodium Pantothenate	10 mg.
Niacinamide	50 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 micrograms
Folic Acid	3 mg.

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY Pearl River, New York

*REG. U.S. PAT. OFF.

a new topical anesthetic for oral administration

XYLOCAINE® VISCOUS ASTRA

(Brand of lidocaine*)

the most effective anesthetic

for the proximal parts of the digestive tract

- Quick acting with prolonged effect
- High viscosity and low surface tension permit the anesthetic, Xylocaine Hydrochloride, to come into immediate and intimate contact with the mucous membranes
- Safe . . . nonirritating . . . nonsensitizing.
- Cherry flavored . . . pleasant and easy to take.
- Xylocaine Viscous has proved valuable in the "dumping" syndrome, hiccup, pyloric spasm caused by peptic ulcer, stomatitis, pharyngitis, esophagitis, acute cardiospasm, pylorospasm in infants, severe vomiting of pregnancy, esophagoscopy, gastroscopy, gastric intubation and gastric lavage.
- Contains 2% Xylocaine Hydrochloride in an aqueous solution adjusted to a suitable consistency with carboxymethylcellulose. Cherry flavored for palatability.

Supplied: In bottles of 100 and 450 cc.
Average Dosage: One tablespoonful, administered orally.
Additional information available upon request

ASTRA

Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.

*U.S. Patent No. 2,441,498

forestall
otitis
media
with

Tyzine

brand of tetrahydrozoline hydrochloride

and eustachian

for nasal patency
in minutes
for hours

new standard for nasal decongestion

- acts promptly, sustains relief for 4 to more than 6 hours after a single administration[1,2]
- odorless, tasteless, neither stings nor burns
- no "rebound" congestion or other local reactions
- rarely causes systemic effects in recommended dosage

supplied: TYZINE Nasal Spray, in 1-ounce plastic spray bottles containing 15 cc. of an aqueous solution of TYZINE, 0.1%; TYZINE Nasal Solution, in bottles of 1 ounce, 0.1%.

1. Parish, F. A.: M. Times 82:917, 1954.
2. Menger, H. C.: New York J. Med., Mar. 15, 1955.

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

. . . no two hypertensives are alike

Harry Webster does much better on Rauvera

Diagnosis: Hypertension Grade II.

H. W., lawyer, 60, was on Veratrum alkaloids (alkavervir) 20 mg. a day for 12 months. Average blood pressure 160/110, pulse rate 70. Vomited once weekly. On Rauvera (3 mg. biologically standardized Veratrum viride fraction – alkavervir – plus 1 mg. purified Rauwolfia alkaloids – alseroxylon fraction – per tablet) 2 tablets a day, in divided doses, for six months, blood pressure dropped to average of 140/95, pulse rate 65. Vomiting reduced to once every 2 months – no postural hypotension. ***Combination therapy*** of alkavervir plus alseroxylon proved clinically superior, with reduced side effects.

Rauvera® is a DORSEY preparation. Supplied in bottles of 100, 500, and 1,000 tablets.

Smith-Dorsey • Lincoln, Nebraska • A Division of The Wander Company

H. W. does much better on Rauvera . . . for no two hypertensives are alike.

Areas of Clinical Study / One of a Series

ANEMIA OF PREGNANCY

Maintenance of normal blood values during pregnancy is a factor in the welfare of the mother at delivery and in preventing anemia in the infant. Improvement in the patient's vitality and emotional stability during gestation can also be achieved.

RONCOVITE, *the original, clinically proved cobalt-iron product, has introduced a wholly new concept in the prevention and treatment of anemia. It is based on the unique hemopoietic stimulation produced only by cobalt. The application of this new concept routinely in pregnancy practically insures against the development of iron-deficiency; its use has also led to marked, dramatic advances in the successful treatment of many of the anemias.*

In a recent clinical study of anemia in pregnancy, Holly[1] *reports:*

—about 80 per cent of normal patients manifest significant decreases in hematologic values during pregnancy.

—conversely, 90 per cent of pregnant women maintained hemoglobin levels of 12 Gm. per cent or over when given Roncovite (iron-cobalt therapy). No other medication tested was so successful.

—in fact, 63 per cent of these Roncovite treated patients delivered with the unusually satisfactory level of 13 Gm. per cent hemoglobin.

—Roncovite (iron-cobalt therapy) has proven to be the most effective hematinic for maintaining an adequate hemoglobin level.

RONCOVITE IS A SAFE DRUG

In pregnancy—"No toxic manifestations associated with its use have been observed."[1]

In prematures—"None of them showed harmful effects despite the large doses..."[2]

In pharmacology—"Histopathologic studies of rats that received cobaltous chloride... revealed no significant degenerative changes in parenchymal organs as evidence of toxicity."[3]

SUPPLIED:

RONCOVITE TABLETS

Each enteric coated, red tablet contains:
Cobalt chloride..... 15 mg.
Ferrous sulfate exsiccated... 0.2 Gm.

RONCOVITE-OB

Each enteric coated, red capsule-shaped tablet contains:
Cobalt chloride..... 15 mg.
Ferrous sulfate exsiccated... 0.2 Gm.
Calcium lactate..... 0.9 Gm.
Vitamin D..... 250 units

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:
Cobalt chloride
(Cobalt 9.9 mg.)..... 40 mg.
Ferrous sulfate..... 75 mg.

DOSAGE:

One tablet after each meal and at bedtime. Children 1 year or over, 0.6 cc. (10 drops); infants less than 1 year, 0.3 cc. (5 drops) once daily diluted with water, milk, fruit or vegetable juice.

1. Holly, R. G.: Anemia in Pregnancy, Paper read at the Sixth American Congress on Obstetrics and Gynecology, Dec. 13-17, 1954, Chicago, Illinois.
2. Quilligan, J. J., Jr.: Texas State J. Med. *50:* 294 (May) 1954.
3. Hopps, H. C.; Stanley, A. J., and Shideler, A. M.: Polycythemia Induced by Cobalt, Amer. J. Clinical Path. *24:* (Dec.) 1954.

Bibliography of 192 references available on request.

RONCOVITE

The original, clinically proved cobalt-iron product

LLOYD BROTHERS, INC.
Cincinnati, Ohio

In the Service of Medicine Since 1870

. . . no two hypertensives are alike

Paul Picard is much improved with Rautensin

Diagnosis: Hypertension Grade II.

P. P., plant foreman, 33. On parenteral hexamethonium 100 mg., and hydralazine 200 mg. a day for 12 months. Reduction of blood pressure (160/120) and pulse rate (80) not too satisfactory. Postural dizziness, constipation and fatigue were main complaints. Regimen was changed to parenteral hexamethonium 100 mg. plus Rautensin 2 tablets a day. (Each Rautensin tablet contains 2 mg. of purified Rauwolfia alkaloids—alseroxylon fraction.) As a result, blood pressure averages were reduced to 150/100, pulse rate to 70. Postural dizziness, constipation and fatigue were completely alleviated.

Rautensin* is a DORSEY preparation. Supplied in bottles of 100, 500, and 1,000 tablets.

Smith-Dorsey • Lincoln, Nebraska • A Division of The Wander Company

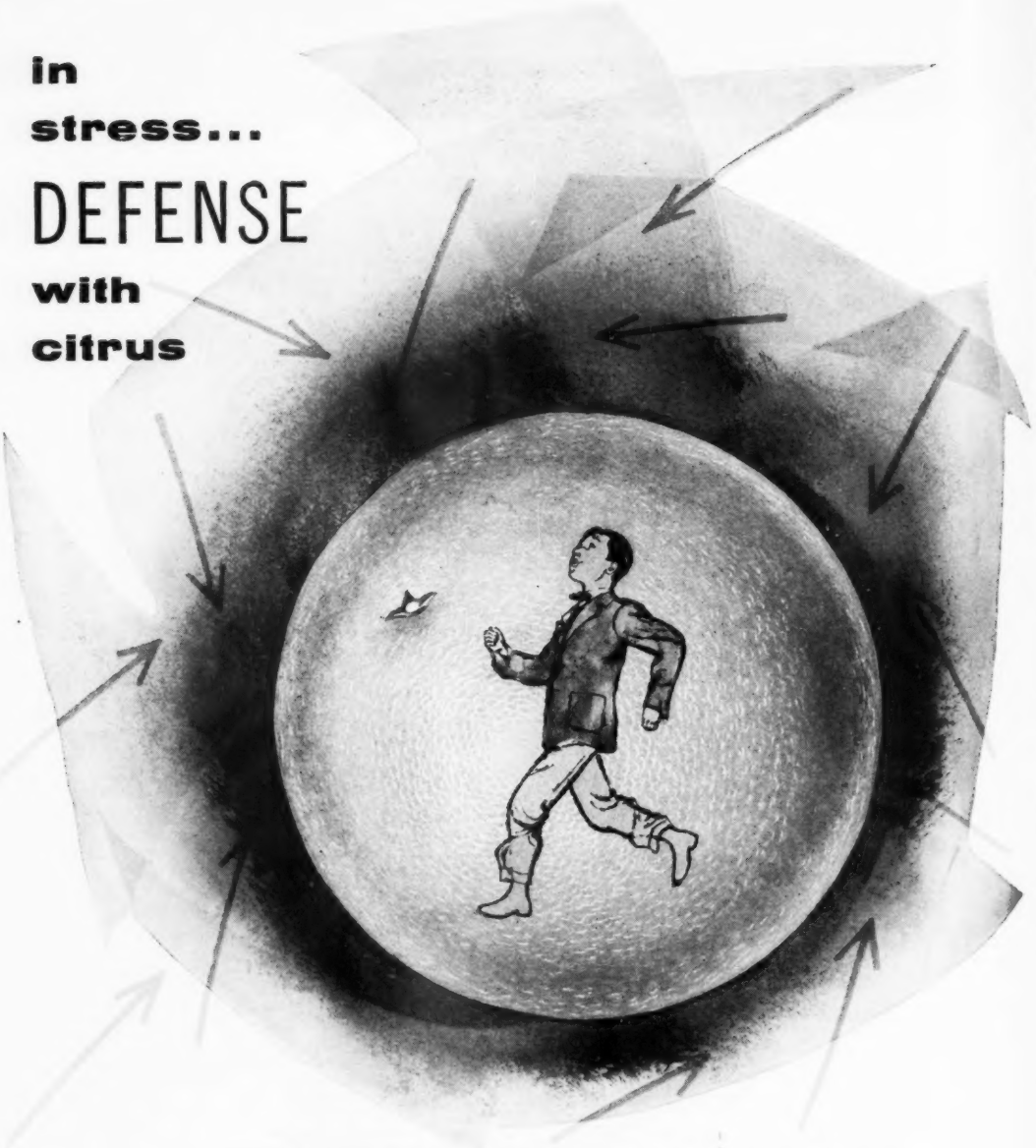
*TRADE MARK

P. P. is much improved with Rautensin . . . for no two hypertensives are alike.

in stress...

DEFENSE

with citrus



Maintenance of adrenocortical function as a cornerstone of resistance in stressful life situations helps prevent disorders characteristic of the general adaptation syndrome. Since vitamin C is essential to production of anti-stress hormones by the adrenal cortex, an ample intake of readily utilized *natural vitamin* C as provided by citrus fruits and juices is desirable.

FLORIDA CITRUS COMMISSION • ***Lakeland, Florida***

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES

. . . no two hypertensives are alike

Eleanor Bradley is "a different woman" on Crystoserpine

Diagnosis: Hypertension Grade I, labile.

E. B., department store buyer, 46. Previously on barbiturates: This was unsatisfactory because of "hangover" and inconsistent blood pressure reductions. Later put on Crystoserpine (crystalline reserpine) 1 tablet 0.25 mg. per day. This resulted in gradual but steady reduction of blood pressure 40 to 45 points below the level achieved with barbiturates. Pulse rate similarly reduced by 10 beats. Anxiety and headaches have decreased, she sleeps more soundly. When fatigued on awakening, an extra cup of coffee quickly relieves this side effect.

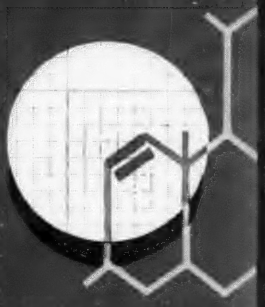
Crystoserpine* is a DORSEY preparation. Supplied in bottles of 100, 500, and 1,000 tablets.

Smith-Dorsey • Lincoln, Nebraska • A Division of The Wander Company

*TRADE MARK

E. B. does better on Crystoserpine . . . for no two hypertensives are alike.

announcing
a new era in
corticosteroid therapy



METICORTEN

METACORTANDRACIN SCHERING

two new crystalline
adrenocorticoids
first discovered and
introduced by Schering

In a planned search for more effective substances without undesirable actions, two new crystalline corticosteroids have been discovered in Schering's research laboratories.

Possessing three to five times the therapeutic effectiveness, milligram for milligram, of oral cortisone or hydrocortisone in rheumatoid arthritis, other so-called collagen diseases, intractable asthma and other allergies, and nephrosis, METICORTEN and METICORTELONE are strikingly devoid of undesirable side actions, particularly sodium retention and excessive potassium depletion. Patients treated with these new steroids do not exhibit fluid retention, and sedimentation rate is lowered even where cortisone or hydrocortisone ceases to be effective—"cortisone escape." These new compounds afford better relief of pain, swelling and tenderness, diminish joint stiffness and are effective in small dosage.

N.....*and* METICORTELONE

METACORTANDRALONE SCHERING

METICORTELONE, which resembles METICORTEN in clinical effect, is now being studied and will be available as soon as possible. The therapeutic properties of both drugs are being studied in other fields of therapy.

The first of these, METICORTEN, is being made available as 5 mg. tablets, bottles of 30. In the treatment of rheumatoid arthritis, dosage of METICORTEN begins with an average of 20 to 30 mg. (4 to 6 tablets) a day. This is gradually reduced by 2½ to 5 mg. until maintenance dosage of 5 to 20 mg. is reached. The total 24-hour dose should be divided into four parts and administered *after meals and at bedtime*. Patients may be transferred directly from hydrocortisone or cortisone to METICORTEN without difficulty.

METICORTEN,* brand of metacortandracin.
METICORTELONE,* brand of metacortandralone.

SCHERING CORPORATION • BLOOMFIELD, N. J.

SCHERING

*T.M.

You don't need a crystal ball, doctor, to choose the best diagnostic instruments

Each Welch Allyn illuminated instrument incorporates in its design all that you need and expect for great accuracy and speed of diagnosis, combined with the durability which means trouble-free long life. Two generations of doctors have proved that.

But you get more than just individual excellence when you choose Welch Allyn instruments. For all those shown here, plus many more, are instantly interchangeable on a single battery handle, a feature which can save many minutes of the physician's time each day, as well as reducing instrument investment by making it unnecessary to purchase a different handle for each instrument.

These are the reasons, we think, why doctors use more Welch Allyn illuminated instruments than any other kind. Your surgical supply dealer will be glad to give you full information on any of the 60-odd fine instruments we now make.

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WELCH ALLYN, INC. • SKANEATELES FALLS, N. Y.

Dear Doctor:

You, like most physicians, are constantly on the lookout for the best product for the purpose intended. This, too, is our objective.

Now we believe we have come very close to hitting the target with the discovery of a new non-barbiturate sedative-hypnotic called Noludar. This new compound, a piperidine derivative, usually brings sleep in half an hour, and its action lasts an average of six to seven hours. Clinical studies in over three thousand patients suggest little, if any, likelihood of hangover or other aftereffects.

You will be interested to know that, in smaller doses, Noludar is an effective sedative for daytime tension. This is important because some physicians feel that a good daytime sedative will frequently eliminate the need for a hypnotic.

Many pharmacies can already fill your prescriptions for Noludar. Others will soon be receiving their introductory stock.

If you would like to try Noludar before prescribing it, just return this letter with your request.

Sincerely,

R. A. Hardt
Vice President

RAH/nt

P.S. This letter, announcing Noludar, was mailed to most practicing physicians. In case you overlooked it, you may be interested in this copy.

Hoffmann - La Roche Inc.
Roche Park, Nutley 10, N. J.

New product... for triple attack on smooth muscle spasm

TRI-SYNAR

Tri-Synar—predominantly a parasympathetic sedative—combines anticholinergic, antihistaminic and direct musculotropic action for better control of spasm.

Tri-Synar works like this:

Drugs in Tri-Synar →	*Produce these effects* →	*For better control of spasm*
Belladonna	Excellent anticholinergic effect Antihistaminic effect	Triple synergism produces excellent belladonna effect with fractional doses of belladonna and minimal side actions
Phenyltoloxamine	Excellent antihistaminic effect Low toxicity (drowsiness remarkably rare) Atropine-like effect	
Ethaverine	Musculotropic effect Excellent inhibition of smooth muscle spasm of gastrointestinal and biliary tracts Atropine-like effect Free of addicting properties	

Each Tri-Synar tablet contains:
Powdered Extract of Belladonna*..... 4.1 mg.
Phenyltoloxamine Dihydrogen Citrate.....20.0 mg.
Ethaverine Hydrochloride.....20.0 mg.
1 tablet t.i.d. or q.i.d.; in more severe cases, 2 tablets t.i.d.

*The amount of belladonna is equivalent to 2.5 minims of tincture of belladonna.

Bottles of 100

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

Hycodan®

(Dihydrocodeinone Bitartrate)

BETTER THAN CODEINE **FOR COUGH**[1]

Syrup (5 mg. per teaspoonful
Oral Tablets (5 mg. per tablet
May be habit-forming. Averag
adult dose, 5 mg. t.i.d. p.c.

BETTER THAN CODEINE *PLUS* APC **FOR PAIN**[2]

Percodan®*

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

FASTER
• LONGER-LASTING
• MORE THOROUGH

Scored, yellow oral tablets. Ma
be habit-forming. Average dose
1 tablet q. 6 h.

1. Hyman, S., and Rosenblum, H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W. Indust. Med. 23:510, 1954.

*U.S. Pat. 2,628,185

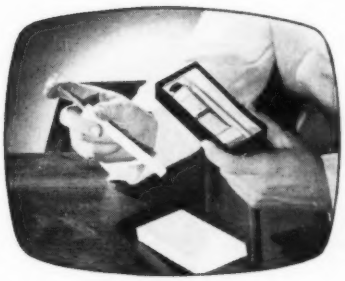
Endo®

Literature? write
ENDO PRODUCTS INC.
RICHMOND HILL 18, NEW YORK

AVC IMPROVED for T.V.

(TREATMENT OF VAGINITIS)

"...but why should **I** have this trouble?"
"Vaginitis is not at all rare, and there are three common causes. Fortunately, we have one simple treatment effective for every type: **AVC** cream."



"With **AVC** cream you can expect relief of discomfort **promptly.** Continue treatment for a month to make doubly certain that the infection is eliminated **completely.**"

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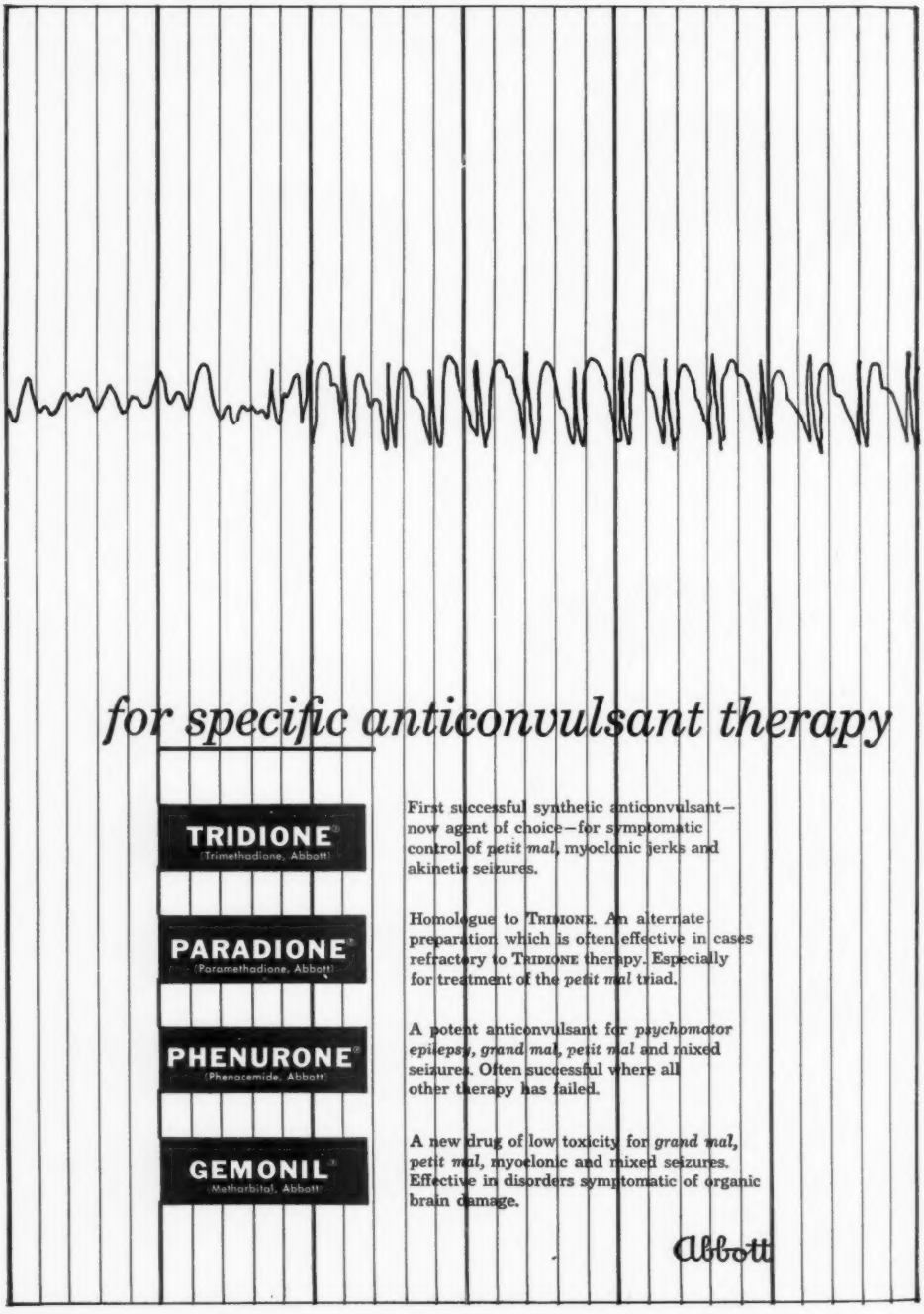

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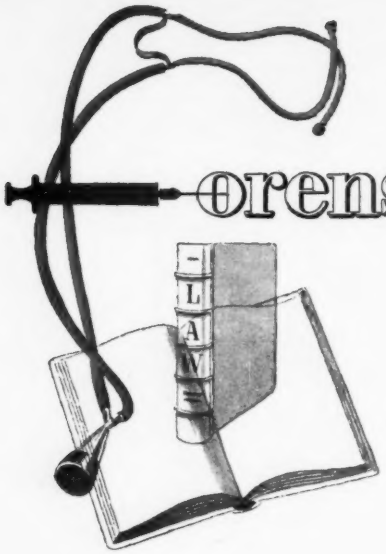

Forensic Medicine

Editors

Dr. Thomas A. Gonzales
Dr. Milton Helpern
Dr. Samuel A. Levinson

"Must I Testify in Court?"

VICTOR H. MILES*

A SUBPOENA is served on you to testify at the trial of your patient who sustained injuries in an accident. Are you aware of your responsibility?

In the usual case, the attorney requests your appearance without a subpoena. However, when you have refused to appear willingly and have justified this refusal because of your busy practice, you are amenable to the process of the court by the service of a subpoena and the payment of a nominal witness fee of approximately one dollar.** This order of the court requires you to appear early on the day of trial, to wait until the case has been assigned to a particular judge and until your testimony is required in the proper presentation of the case. Several hours or even days may elapse with a substantial loss of income for which you are not reimbursed. If you offer your services promptly and affably, these consequences will be avoided.

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Doctors who themselves have been litigants requiring the aid of other physicians are fully aware from their own experiences of the importance of medical evidence, and thereafter are most gracious and sympathetic in furnishing their testimony for the benefit of patients. An appreciation of the difficulties confronting the litigant and his attorney will aid the administration of justice. Cooperation from doctors is essential. It will foster a cordial relationship with members of the bar and a respectful gratitude from patients.

Often doctors have refused to testify until their bills have been paid. If the patient is indigent, the bill is uncollectible. The doctor can be magnanimous by offering his testimony and obtaining payment of the bill if there is a successful recovery, or the doctor can refuse to testify, in which case the advocate has no alternative but to serve a subpoena. If the patient is neglectful rather than destitute, the judge, in the

(Continued on page A-58)

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*Trial Attorney, Newark, New Jersey; Associate Editor in Tort, National Association of Compensation Claimants' Attorneys; Contributor to *New Jersey Law Journal*.

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If you must or desire to appear for either side, it is suggested that you immediately call the attorney and request that you be placed "on call." If you leave word where a message can be transmitted, the attorney will have you summoned after the trial has commenced and only when that phase requiring your testimony has been reached. Thus, upon your arrival at the courthouse you will be immediately placed on the witness stand. If your schedule calls for your attendance at an operation, your testimony may be received out of order by special permission of the court.

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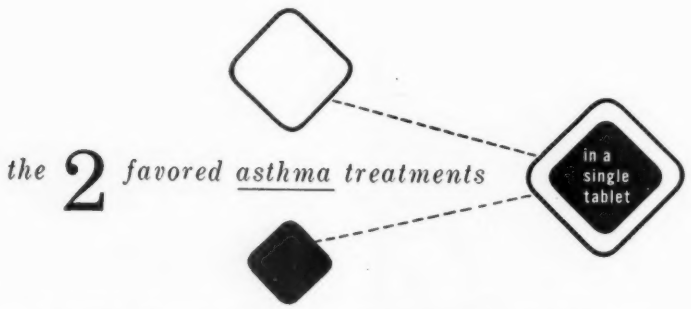
There are two types of subpoenas. A subpoena *ad testificandum* merely requires your oral testimony. A subpoena *duces tecum* requires that you testify and bring with you the pertinent records described therein. Regardless of which type is served, it behooves you to have available in court all of your original records. They may be in the form of a single card with chronologic entries or several independent and unrelated memoranda. The latter may be collated for the purpose of clarity and to reveal continuity of treatment, but always have with you the original notations.

It is a dangerous risk for the doctor about to testify to make a new record of his treatments because he has destroyed his original notes. It is sheer folly for the doctor who finds his charts and records inadequate and incomplete just prior to a trial to interpolate information thereon to remedy any deficiency. This topic will be discussed in greater detail at a later date.

*Specific requirements vary according to local law.

This is the first of a series of articles whose aim is to familiarize the practitioner with the requirements of the law in personal injury trial practice.



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1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, Mar. 22, 1952.

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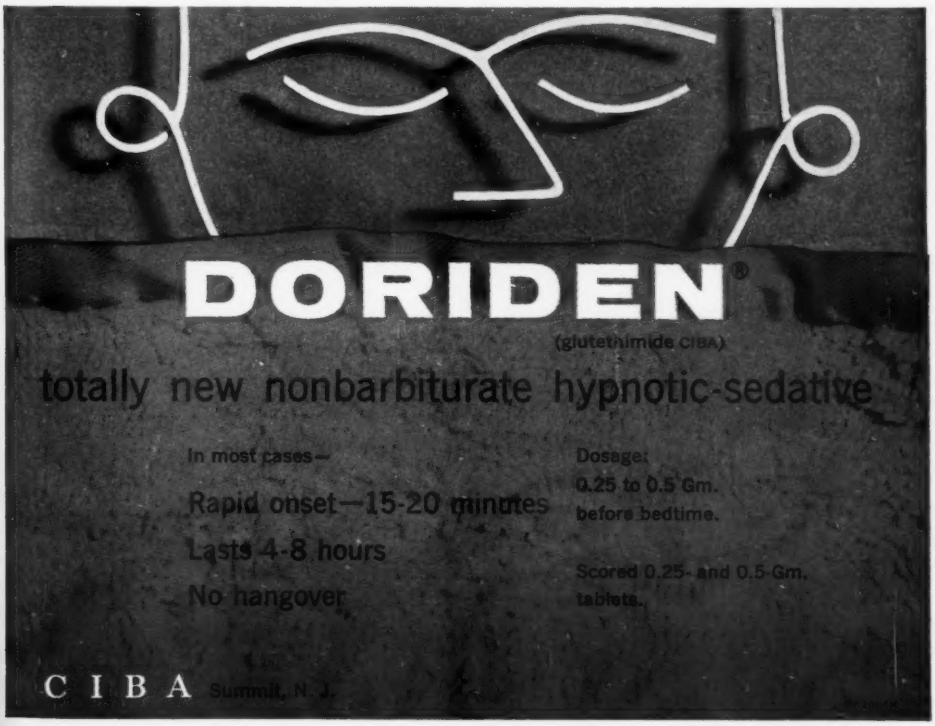

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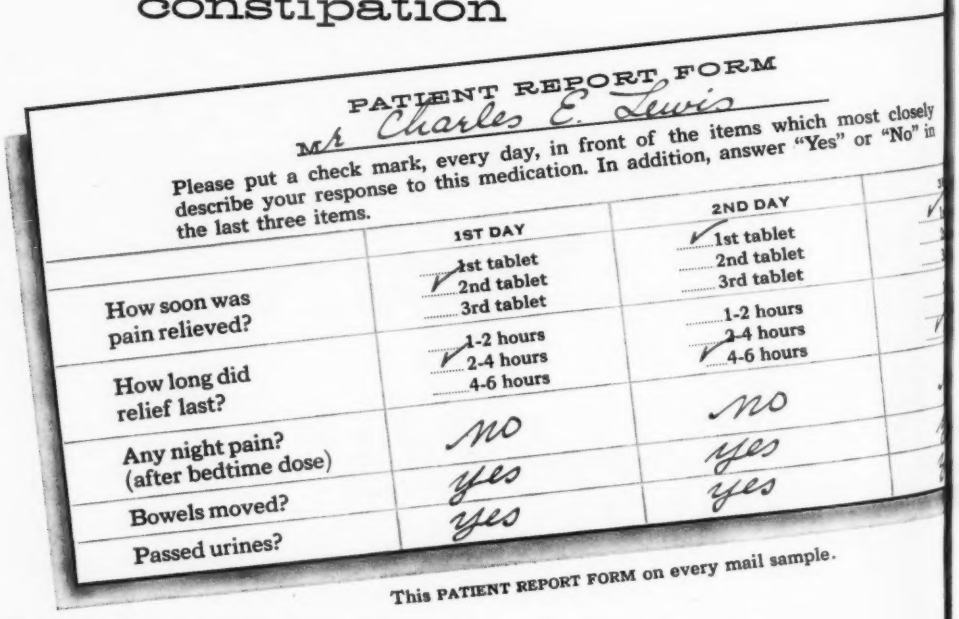

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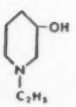

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Uveitis as a Medical Problem

(THE SCHNEIDER FOUNDATION EYE PRESENTATION)

F. PHINIZY CALHOUN, JR.*

Emory University School of Medicine, Atlanta

F. PHINIZY CALHOUN, JR.

THE purpose of the annual Schneider Foundation Eye Presentation is to outline the development of research and to report scientific progress on some ophthalmologic subject with particular reference to constitutional diseases and their effect on the eye. I respectfully hope this presentation will follow the example so ably set by previous speakers.

My remarks are not directed to ophthalmologists alone or to internists alone, but to all physicians dedicated to the care of patients.

The human body has many ways of expressing poor health, and one of the frequent and quite disturbing ways is by the development of endogenous uveitis. The investigation and treatment in a case of uveitis are examples of still another common meeting-ground for the ophthalmologist and physicians in other fields, especially internal medicine.

Before deciding how and why uveitis is a medical problem of general interest, let me define it in clinical terms. The uvea, or uveal tract, is a highly vascular and pigmented tissue of the eye, unique and not simulated by any other tissue of the body. The anterior uvea is composed of the iris and ciliary body; the posterior uvea is called the choroid. Inflammation may involve one or all of these structures under the loose term "uveitis."

The type of uveitis under consideration here is the common endogenous uveitis. Not included is the less common but more obvious and destructive pyogenic metastasis to the eye which quickly develops into endophthalmitis or panophthalmitis. Also excluded is uveitis due to ocular injury, as seen in sympathetic ophthalmitis.

Ordinary endogenous uveitis, then, of one

*Department of Ophthalmology, Emory University School of Medicine; Grady Clay Memorial Eye Clinic, Grady Memorial Hospital, Atlanta, Georgia.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

type or another, is a very common condition and a very serious and incapacitating one. National and international statistics[1] show that 15 per cent of blind persons lost their vision because of uveitis, and that correlation of the clinical and pathologic diagnoses is frequently erroneous. Uveitis is quite a serious military problem, since the protracted course in many cases requires a longer hospitalization than for other eye patients. A recent survey at the Walter Reed Hospital[2] showed that patients primarily admitted because of uveitis accounted for 5 to 10 per cent of all admissions for eye diseases.

Careful evaluation by the ophthalmologist of the clinical findings in cases of uveitis can provide valuable clues concerning the underlying process. Present-day clinical efforts are directed toward distinguishing between granulomatous and nongranulomatous forms of uveitis, since these terms have become so ingrained in American ophthalmologic literature. These terms are not accepted in Europe on the ground that they are actually pathologic terms and should not be used to describe pathogenic and clinical differences, especially since histologic differentiation often may be impossible.[3, 4]

When present in pure form, the two types of reaction are easily recognizable. Often, however, they are combined, making differentiation difficult. The important reason for clinical distinction is that often it provides a clue as to the cause of the condition.

In typical endogenous granulomatous uveitis we presume a direct invasion of the uvea by some living bacterial agent or virus. When this occurs in the anterior uvea, i.e., the iris or ciliary body, there results a low-grade, quiet inflammation of the iris, with inflammatory nodules on the surface of the iris and numerous greasy precipitates on the posterior corneal surface. When the process begins in the choroid, or posterior uvea, the lesion has a characteristic localized exudative reaction and the vitreous cavity becomes clouded with stringy opacities.

Endogenous nongranulomatous uveitis is believed to be the result of a sterile toxic or allergic reaction and in most cases probably is due to an underlying bacterial hypersensitivity. The typical clinical manifestations are quite different from those just described. The reaction in the anterior uvea is acute and violent. The inflamed iris easily develops adhesions to the lens. There are no nodules on its surface and no large, greasy posterior corneal precipitates. Recurrent attacks are common, each one adding to the damage of the previous attack and thus gradually destroying vision. When the posterior uvea or choroid is primarily involved, the overlying retina is intensely edematous, there is no exudation, and the vitreous is relatively clear.

In their uncomplicated forms the differential clinical diagnosis of these two disease entities may be easy, but in the combined or complicated forms it may be difficult, even histologically. According to Woods,[3] "This difficulty arises from the fact that in basic granulomatous uveitis, there may be a superimposed allergic nongranulomatous reaction, and in nongranulomatous uveitis, when the allergic insult is prolonged, both the clinical and histological pictures may simulate a granulomatous process. Thus the final end-stages of both conditions may appear similar, despite a different pathogenesis."

The systemic conditions which commonly produce a primarily granulomatous uveitis are tuberculosis, sarcoidosis, brucellosis, syphilis and toxoplasmosis. Less commonly implicated are certain diseases due to virus infections and supposed virus infections.

Granulomatous Diseases Producing Uveitis

Tuberculosis

In Europe the incidence of chronic uveitis reported as due to tuberculosis is much higher than in this country. As a matter of fact, opinions among ophthalmologists in this country differ greatly concerning the incidence, clinical manifestations and diagnostic criteria of ocular tuberculosis. Specific cases considered tuberculous in one locality would not be so designated in others. The true incidence of chronic ocular tuberculosis is unknown, but it is well recognized that ocular involvement is

rare among patients in tuberculosis sanatoria. Cases of tuberculous uveitis proved either by histologic demonstration of the bacilli or by guinea pig inoculation are very rare. Histologic sections of proved cases are very difficult to get for teaching collections.

The diagnosis of tuberculous uveitis must always be a presumptive one based only on indirect evidence. According to Woods,[5] the diagnosis must rest on four points: (1) the clinical picture, whose varied manifestations are beyond discussion here; (2) the exclusion of other possible etiologic factors, which implies the necessity for a thorough clinical and laboratory work-up in every case of uveitis; (3) the demonstration of a systemic reservoir whence the ocular infection may have arisen. In only about 50 per cent of cases of presumptive ocular tuberculosis are there positive roentgenologic evidences of old pulmonary infection. A mediastinal reservoir (old hilar glands) is probably the most common source of infection; (4) the tuberculin reaction. It must be remembered that in a tuberculous subject without ocular disease, skin sensitivity and eye sensitivity are parallel. However, if an ocular focus is present, the ocular sensitivity will be high whereas the cutaneous sensitivity may be low or absent. Therefore, if the tuberculin reaction is strongly positive, the test is of great diagnostic value. However, a low or absent reaction means nothing, and unfortunately about 30 per cent of cases of ocular tuberculosis fall in this category.[5]

Tuberculin testing in suspected cases should always be performed with the weakest strength available, since a severe cutaneous reaction reportedly has produced a serious flare-up in true tuberculous uveitis. Ophthalmologists prefer to use old tuberculin, which is considered less potent than PPD (purified protein derivative). In using PPD it must be remembered that the second strength test dose is 250 times stronger than the first dose.

In recent years an enormous amount of work has been done on the effect of various drugs on experimental tuberculous uveitis in animals. The severe exacerbation or "rebound phenomenon" appearing in tuberculous infections following cessation of therapy with cortisone has been mentioned by Schlaegel[6] as a reason for not giving cortisone to patients with tuberculous uveitis, but should this phenomenon occur it is of possible diagnostic value. The development of the newer chemotherapeutic agents in the treatment of general tuberculosis has been followed experimentally and clinically in ocular tuberculosis, and reports are favorable. It was recently found[7] that isoniazid is relatively nontoxic, passes readily across the blood-aqueous barrier, and is easy and economical to take in tablet form. For tuberculous uveitis the recommended dosage is 3 to 5 mg. per kilogram of body weight per day, with continuation of therapy for several months after evidence of activity. In tuberculous uveitis this drug, which is bacteriostatic only, should be used in conjunction with other antituberculous measures, such as streptomycin and dihydrostreptomycin, PAS, tuberculin desensitization and physical rest.

Sarcoidosis

Inflammation of the uvea is very common in sarcoidosis, and the usual lesion is a granulomatous or nodular iritis. When the uveitis is associated with parotitis and skin lesions, and frequently with paralysis of one or more cranial nerves, the syndrome is called uveoparotid fever or Heerfordt's disease. The uveitis may be the chief or even sole clinical manifestation of sarcoidosis. Although the presence of skin nodules, x-ray changes in chest and long bones, negative tuberculin test, and reversal of albumin-globulin ratio are to be looked for as characteristic findings in the general disease, the biopsy of even a normal-sized preauricular, postauricular or cervical lymph node will often clinch the diagnosis.

Brucellosis

A granulomatous iritis and a spotty type of exudative choroiditis can occur during the course of brucellosis, but the diagnosis of brucellosis, much like that of tuberculosis, is a presumptive one. Recurrent attacks of uveitis, a history of low-grade fever and of the ingestion of raw milk, and the isolation of *Brucella* organisms from blood, pockets of infection, or sternal bone marrow all suggest

the diagnosis of brucellar uveitis. One big problem in the diagnosis is the reliability and interpretation of the usual agglutination tests, skin test and the phagocytic opsonic index. What percentage of cases of endogenous uveitis can be proved to be due to brucellosis remains to be determined.

Toxoplasmosis

There is currently a great interest in the study of human toxoplasmosis, especially its manifestations as an acquired disease in the adult and its relationship to certain forms of uveitis. It has been recognized for some time that a prenatal infection with *Toxoplasma* organisms produces a severe disease in the newborn infant consisting of encephalitis and chorioretinitis, which result in mental retardation, blindness and other defects. In 1952 Wilder[8] discovered in histologic sections of adult cases of chorioretinitis organisms having the characteristics of *Toxoplasma*. Her observation renewed the interest in toxoplasmosis as a cause of uveitis in adults. The ultimate isolation and identification of live parasites from a typical clinical case of adult uveitis recently was reported by Jacobs, Fair and Bickerton.[9] The etiology in this case was established beyond question. These developments indicate that many cases of granulomatous uveitis are probably due to toxoplasmosis, especially many cases which are now classified as tuberculous.

Not much is known yet about the general clinical manifestations of toxoplasmosis, except that they may be very mild and quite variable. Interpretation of laboratory tests is undergoing clarification. Of great interest is the information that the new skin test for this disease, utilizing antigen made from mouse peritoneum, is much more reliable than the former test which employed egg embryo antigen. There is promise that this antigen will soon be available commercially. The Sabin-Feldman dye test is the important serologic test in cases of suspected toxoplasmosis. It is difficult to get such tests performed, especially in series. Except for a few state laboratories or institutions doing research on toxoplasmosis, the United States Public Health Service is the only place where the tests are made, and facilities are not available to handle the number of tests required for eye cases.

Leptospirosis

An increasing number of reports are appearing on the eye involvement in human leptospirosis.[10,11] The acute iritis and sometimes granulomatous iridocyclitis occur as late manifestations of leptospiral infection. They may first appear from three weeks to one year following the original infection but the average onset is in from four to eight months. The uveitis has no specific clinical picture but is prone to recurrences and can lead to blindness. The organisms can be cultured from the aqueous humor. Of the several strains of *Leptospira*, *Lept. pomona* and *Lept. icterohaemorrhagiae* seem to involve the eye most frequently. A presumptive diagnosis can be made from the history and the serologic findings. The serum agglutination reactions are again rather difficult to obtain except in a few laboratories or institutions conducting research in leptospiral disease. An extended mass survey of cases of iridocyclitis has not yet been carried out, but reports on a series of tests performed on a group of soldiers with iridocyclitis showed only a very low incidence of leptospirosis.

Uveitis associated with joint disease

Articular disease in children, as in Still's disease, not uncommonly has the late complication of quiet, bilateral iridocyclitis, band keratopathy and complicated cataract. The uveitis is frequently not discovered until it has progressed to marked posterior synechia and is very difficult to treat. Tragically, removal of the cataract in such cases is invariably unsuccessful and the eye becomes phthisic. In young adults a severe, recurrent, violent form of plastic nongranulomatous iridocyclitis may be associated with rheumatoid arthritis. Here, again, the late complications are band keratopathy and complicated cataract. In many instances the uveitis may be the first and presenting sign of the Marie-Strümpell type of arthritis so that roentgenograms of the lumbar spine and particularly of the sacro-iliac joint

will disclose early changes in cases of recurrent acute iridocyclitis.

Uveomeningeal syndromes

In recent years there has been much interest in forms of uveitis associated with meningeal signs. One such syndrome is that of Vogt-Koyanagi which has bilateral granulomatous uveitis, retinal detachment, alopecia, poliosis, deafness and variable meningeal signs. Probably a related condition is Harada's syndrome in which the chief finding is bilateral uveitis with retinal detachment, but without the marked signs present in the Vogt-Koyanagi syndrome. A viral origin of these two conditions has been suspected and has been proved in a few reports from the foreign literature.

In Behçet's disease there is characteristically a relapsing iridocyclitis with frequent hypopyon, aphthae of the oral mucosa, and ulceration of the sexual organs. A virus has been isolated from the vitreal and subretinal fluids in at least three cases.[12] Meningeal involvement is frequent.

Nongranulomatous Uveitis

As mentioned previously, the violent, acute reaction of nongranulomatous uveitis is thought to be a sterile hypersensitivity reaction. Locally, in the eye, this may occur secondarily, on the assumption that a previous bacteremia has caused organisms to lodge in the uvea and be killed and thus produce local hypersensitivity to the bacteria. Since the original source may be a focus of infection elsewhere in the body, there arises the question of the significance of foci of infection in nongranulomatous uveitis. The theory of focal infection, long nourished by the ophthalmologist as an explanation for many of these infections, has been gradually outmoded in this country. Many workers have demonstrated that the incidence of infective foci is no higher in cases of uveitis than in patients without uveitis. However, Woods[13] reported recently that 89 per cent of patients with nongranulomatous uveitis showed specific streptococcal hypersensitivity, as compared with 20 per cent in the granulomatous group. Furthermore, he found that specific desensitization of the hypersensitive patient with intravenous streptococcal vaccine was successful in most of these cases. Recently, Leopold and Dickinson[14] demonstrated a tendency for the serum titers of antihyaluronidase and antistreptolysin to be higher in cases of nongranulomatous uveitis than in a control group of normals. We cannot ignore a focus of infection completely if the attacks of uveitis coincide with flare-ups of the focus or if there is a positive reaction to a skin test employing the autogenous vaccine made from the focus.

Endogenous uveitis, in one form, or in a combined form, may occur in a multitude of general infectious diseases and degenerative conditions—syphilis, histoplasmosis, torulosis, lymphogranuloma venereum, coccidiosis, mumps, diabetes and gout, to mention only a few. A specific diagnosis of the general internal condition responsible can be presumed only from the eye manifestations. One realizes the magnitude of the medical problem involved when one considers that in reported analyses of large numbers of cases of uveitis examined by experts in all fields of medicine, with all the diagnostic tools of a large institution, the true cause of the uveitis can be determined in only about one-third. The problem is relatively simple when the case belongs to one of the diseases or disease syndromes I have outlined, but most cases of uveitis seen originally by the ophthalmologist occur as a solitary manifestation in what is found to be a normal, healthy young person with no unusual history and a normal physical examination. The patient is told that the condition comes from some internal disturbance and he cannot understand when all the tests and examinations are negative or inconclusive. He expects modern medical science to find the cause, but how often are both patient and physician disappointed!

These facts mean to me that the process involved is an extremely subtle one that escapes ready recognition, and that our vigilance and efforts must be further exerted to find still newer process at fault. They mean that our laboratory and serologic aids must be improved and made more generally avail-

able and that newer and more specific diagnostic tests must be developed. They also indicate that the study of a case of uveitis requires the cooperation of men in all fields of medicine.

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Postgraduate Clinical NOTES

32. CONSTITUTION

Every human being who is not one of a pair of identical twins is uniquely different from every other human being. Probably every single one of us has genetic characters which he would be healthier without. And every doctor will agree that in one way or another the patient's "constitution" is concerned in his every illness. Also intrinsic to the individual in the sense I am using the word is his emotional attitude toward his environment. A man's temperament is probably very largely inborn, but at any given point in his life it is what his life's experience has made of his inherited make-up. There is no doubt that many diseases are psychogenic in origin—i.e., they would not have occurred if the patient had not been exposed to worry, frustration, and other non-material impacts of the environment. Equally we can feel certain that there are people whose inheritance is such that no conceivable amount of frustration or fear would induce peptic ulcer or chronic colitis. Finally we have to recognise that death *is* a necessary end—a universal evolutionary necessity—and to die is as much part of our inheritance as to cease growing at 18 or 20. The healthiest of men finds his tissues hardening and failing as he passes 70, and in one place or another the final breakdown will come eventually. The rate of senile degeneration in different tissues will vary from person to person, presumably mainly for genetic reasons.

MacF. Burnet, *Lancet*, January 17, 1953, pp. 104-108

Male Hypogonadism

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THERE is generally a rather poor understanding of the problem of male hypogonadism because of several reasons. Obvious male hypogonadism is relatively rare. Until recent years the different syndromes were not clearly defined. Many tests, such as hormone determinations, reliable sperm examinations, and histologic interpretations of the testicular biopsy specimens, have not been available to the great majority of practicing physicians. Indifference to and inadequate examination of the male gonads also contribute to the lack of interest in male hypogonadism. As one of our colleagues has so aptly stated, next to the male breasts, male gonads are the most neglected structures during examinations.

As a consequence, many physicians have not developed a clear picture of the normal range of variation of the gonads, genitalia and secondary sex characteristics. There is a wide range of normality. There may be men with relatively small (lower range of normal) gonads who present unmistakable evidence of normal androgenic and gametogenic function. The evidences may include normal adult male voice, beard, body hair, distribution of pubic hair, normal habitus, recession or thinning of scalp hair, and normal semen.

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Morphologic and Physiologic Changes

A brief summary of the morphologic and physiologic changes which occur in the testes during the normal life span follows. The interstitium of the fetal testes (35 weeks) is packed solidly with Leydig cells. These cells disappear completely during the first few weeks after delivery. The Leydig cells then do not become morphologically apparent again until stimulated by endogenous pituitary gonadotropin at the time of puberty. They then remain in normal quantity and appearance until senility, although gradual decrease in number of cells may occur in old age.

In the fetal testes the seminiferous tubule is a small, solid cord. Unlike the intertubular tissue, the tubular tissue does change gradually in the direction of maturity. Beyond the age of six years the germinal cords acquire a lumen, and the germinal syncytium is arranged in a characteristic pattern of two layers of nuclei. The testes remain in this state and are relatively quiescent until puberty when evidence of spermatogenesis usually precedes

appearance of mature Leydig cells. The pituitary gonadotropins (F. S. H. and L. H.) presumably result in stimulation and function of both tubular and Leydig cells.

LAURENTIUS O. UNDERDAHL

A. ALBERT

Classification

There are several recent classifications of male hypogonadism. Heller and Nelson[1] proposed a classification based primarily on the therapeutic response of the patient to chorionic gonadotropin. Howard and associates[2] based theirs primarily on the assay for pituitary gonadotropin. We (Albert and associates) used the histologic picture of the biopsy specimen of the testes as the primary basis for classification.[3] Although the three classification systems emphasize three different procedures, each group used supporting data as obtained from clinical features, hormone assays and testicular biopsy.

It is beyond the scope of this paper to repeat or discuss these classifications. It is also impossible to give diagnostic features of all the recognizable forms of hypogonadism. We would therefore prefer to discuss some of the distinguishing features of various groups and then present data on three illustrative cases. Those who are interested in more details may refer to our series of papers on male hypogonadism.[3-8]

Male hypogonadism is a general term used to denote diminished or absent function of either the Leydig cells or the seminiferous tubules or both, regardless of etiology. Therefore, when confronted with a problem of male hypogonadism one must consider the two distinct anatomic and physiologic portions of the testes. The Leydig cells produce androgens and are responsible for male habitus and secondary sex characteristics. A deficiency of the Leydig cells results in the types of hypogonadism which may be apparent from history and examination. The seminiferous tubules produce sperm but probably have no influence on secondary sex characteristics. Therefore, tubular failure alone (without Leydig cell failure) is usually unsuspected until infertility may lead to investigation.

The many different entities are determined by several factors, such as (1) whether the gonadal failure is primary or secondary to pituitary insufficiency, (2) whether onset of the lesion was prior to or after the patient reached maturity, and (3) whether the deficiency involves the Leydig cells, seminiferous tubules or both.

In the case of primary gonadal failure the testicular tissues sufficiently altered by disease (infection, degeneration, trauma, surgical or congenital absence, and so forth) are unable to respond to endogenous pituitary stimulation or to administered chorionic gonadotropin. In such patients there usually is an increase in pituitary gonadotropin as a consequence of lack of suppression from androgens or lack of testicular tissue on which gonadotropin can act, or of both factors.

If the testicular lesion occurs prior to puberty and involves both tubules and Leydig cells, or Leydig cells alone, it will result in eunuchoid habitus (span greater than height, distance from heel to pubis greater than that from pubis to vertex, and wide female-type hips). If such a lesion occurs after puberty there will only be regression of secondary sex characteristics and the habitus will remain that of the normal male.

If only the tubules are involved, no change in habitus or secondary sex characteristics will occur regardless of time of onset. In general, it might be stated that normal tubular function (normal semen) is usually good indirect evidence of adequate androgens or Leydig cell function. Rare exeeptions to this may occur in certain stages of development of pituitary tumor in the adult and in the so-called "fertile eunuchs" described by McCullagh and associates.[9] Normal Leydig cell function as evidenced by normal secondary sex charac-

teristics and normal urinary 17-ketosteroids, on the contrary, gives no reassurance of normal tubular function. In other words, normal male characteristics do not exclude male infertility. Infertility in an otherwise normal male represents the largest group of hypogonadism.

In the patient with pituitary insufficiency the testes, because of insufficient gonadotropic stimulation, remain in the prepuberal state if the onset is prior to puberty or atrophy if after puberty. The testes in these patients are capable of responding to administered chorionic gonadotropin to produce male hormone.

There are a group of patients, whose condition is referred to by Heller and Nelson[1] as "hypogonadotropic hypogonadism," who have no evidence of pituitary insufficiency except lack of gonadotropins. When this occurs before puberty the clinical picture may be indistinguishable on physical examination from that of the eunuchoid patient with primary testicular failure because growth and other trophic hormones being present allow skeletal growth to continue. The testicular biopsy as well as urinary gonadotropin is usually distinctly different and helpful in differentiating these two syndromes.

Lack of gonadotropic hormone alone (other pituitary hormones adequate) may be idiopathic, may occur in certain stages of a pituitary tumor, or may be a result of pituitary (gonadotropic) suppression by either testosterone or estrogens. If there is panhypopituitarism prior to maturity, then the picture, of course, will be pituitary dwarfism with other end-organ deficiency as well as that of hypogonadism. In the adult in whom panhypopituitarism develops there is loss of secondary sex characteristics and the testicular tissue atrophies, but there is no change in skeletal proportions.

History

As in other fields of diagnosis, a careful chronologic history is imperative in problems of male hypogonadism. A childhood history regarding infectious diseases (particularly mumps), any type of prolonged illness, malnutrition, and so forth, is obtained as well as that of growth pattern. Details regarding puberty, such as time of onset, libido and nocturnal emissions, are recorded. Have the testes always been in the scrotum; if not, at what age did they descend? Is there any history of orchitis, severe trauma or irradiation to testes? If symptoms have occurred following normal development and sexual function, then details as to time of onset and details of symptoms, such as change in libido and potentia, general strength, beard, body hair and size of genitalia are important. We wish to comment that loss of libido and potentia without other objective evidence of androgen lack is most likely psychologic in origin.

Examination

Besides the routine examinations there are several special ones to be noted. Observations should be made of the voice, facial appearance, color and texture of the skin, beard, body and pubic hair and general body proportions. Is the voice normal or high-pitched? Is the facial appearance commensurate with or younger than the patient's age? Pallor and thinning of the skin are common in patients who lack androgens. The pale, smooth, beardless and youthful face of the eunuchoid patient is quite apparent. Later in life there is frequently excessive wrinkling of the skin of the face. Normal beard, axillary, body and pubic hair (male distribution) is an indication of adequate androgens. A lack or loss of such hair may result from inadequate androgens whether due to primary or pituitary Leydig cell failure. Thinning or recession of scalp hair usually indicates adequate male hormone, at least at the time of the hair loss.

Abnormal proportions, such as narrow shoulders, wide hips, short trunk and long extremities, represent the eunuchoid habitus. Careful measurements should be recorded of the height, span, vertex to pubis, and pubis to heel. Actual measurement should also be made of the penis and testes. A change in these is very useful as a criterion for evaluating the result of treatment or progress of puberty. The consistency of the testes, whether normal, soft or firm, should be noted. If the testes are not palpable in the scrotum, can

they be identified in the inguinal regions? Palpate the prostate and estimate whether it is normal, small or nonpalpable. If there always has been lack of androgens, the prostate will likely be nonpalpable. Loss of androgens after maturity will usually result in atrophy of the prostate.

Careful examination of the male reproductive tract is of most importance in puberal boys. When asked to see a boy at age 14 to 16 years by parents who are overly concerned because the son has not developed normally, there are several signs which may be reassuring to parents, patient and physician. The first and most reassuring sign of puberty is the growth of the testes and scrotum (figure 1). Other early signs of puberty, such as acne, development of scrotal rugae, beginning pubic hair, growth of the penis and lowering of the voice, are physiologic evidence of androgen production. If such are present, further progress in the next few months can usually be anticipated. As a consequence of this obvious information, observation, rather than therapeutic intervention, should be carried out. The patient with often-diagnosed "Fröhlich's syndrome" most often is a fat boy with the genitalia and testes partially obscured by obesity. Some may have delay of puberty.

Of importance is the fact that maturity does not occur at a given age for all individuals, but rather may begin at any age from 9 to 19 years (Schonfeld,[10] Greulich and associates,[11] and Nathanson and associates[12]). There is no way to predict the time of onset of puberty in any one individual. Once started, about three years are required for completion of puberty (figure 2).

Laboratory tests—Whatever routine tests are indicated are performed. There may be a low-grade anemia and lowering of the basal metabolic rate associated with androgen deficiency. Both may be improved by the administration of testosterone. Roentgenograms of the sella turcica for evidence of pituitary tumor and of the hands and wrists for bone age are useful in certain cases. Hormone assays (if available) for 17-ketosteroids, corticosteroids, pituitary gonadotropin and estrogens may help in categorizing certain entities while unnecessary in others. Although one refers to F. S. H. and L. H., there is no practical method at present for assaying these separately, but rather they are assayed as gonadotropin. Semen examination should include volume, motility, morphology and the actual

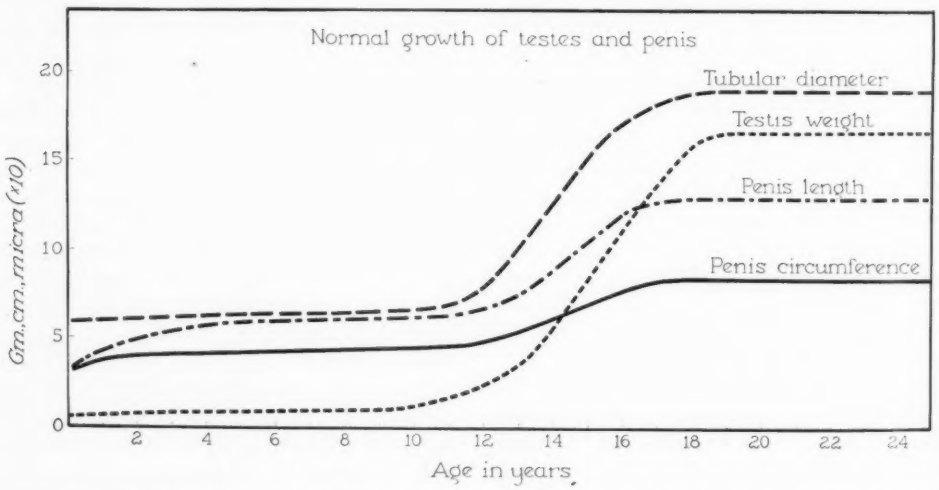

FIGURE 1. Normal growth of testis and penis (from data of Schonfeld) and of tubular diameter (from Albert, A., Underdahl, L. O., Greene, L. F. and Lorenz, Nona: Male hypogonadism. I. The normal testis. Proc. Staff Meet., Mayo Clin. 28:409-422 [August 12] 1953).

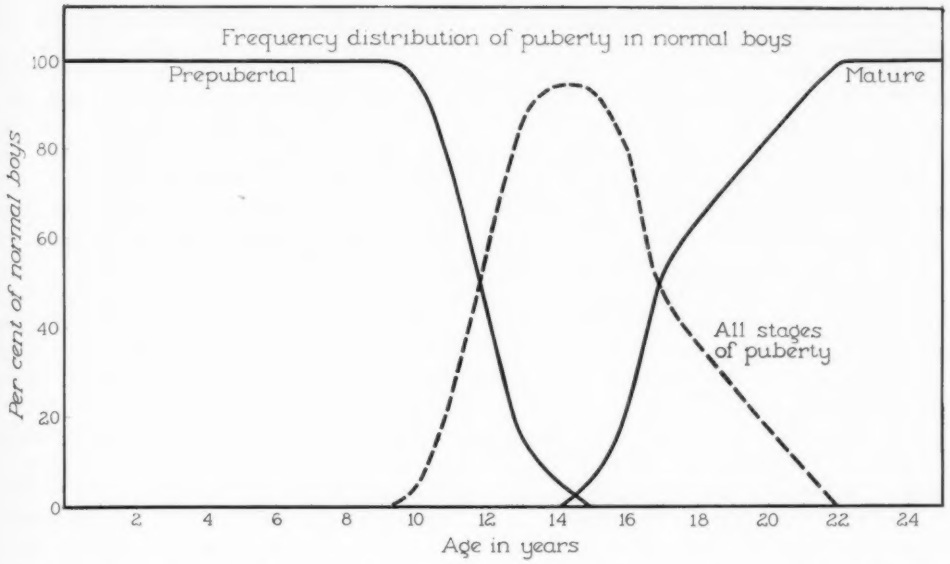

FIGURE 2. Frequency distribution of age at puberty among approximately 2000 normal boys (from data of Schonfeld; Albert, A., Underdahl, L. O., Greene, L. F. and Lorenz, Nona: Male hypogonadism. I. The normal testis. Proc. Staff Meet., Mayo Clin. 28:409-422 [August 12] 1953).

count of spermatozoa. This examination is, of course, of primary importance in investigation for infertility but also, as stated before, usually gives indirect evidence of Leydig cell function.

Biopsy of the testes is performed whenever it is necessary to achieve a final definitive diagnosis of hypogonadism, or to ascertain precisely the state of the germinal epithelium for prognostic information of infertility.

*Case Report—Pituitary Dwarfism**

History—The patient was a 34 year old entertainer who had had episodes of nausea, weakness, vomiting and stupor. He stated that he had been a normal boy until the age of six years, at which time his growth was slowed. At the age of 13 years he was only 39 inches tall. He grew only three and one-half inches after that time. Eruption of his permanent teeth was delayed until the age of 15 years, at which time the deciduous teeth were extracted. After the age of 27 years he had had several spells of weakness and coma lasting for a period of two weeks. During a similar attack at the age of 31 years, he had had "low blood pressure and low blood sugar." He tolerated extremes in temperature poorly. Weakness occurred if breakfast was postponed. He had experienced minimal libido with occasional erections but no ejaculations.

Physical examination—The patient presented an unusual appearance of an old person with a childlike body and a childlike voice. He was 42½ in. tall, and his span was 42½ in. The distance between crown and pubis and pubis and heel was equal, being 21¼ in. The weight was 43 lb. The skin was wrinkled, dry and scaly, and had a yellowish tinge. No axillary, pubic, extremital or facial hair was present. The scalp had abundant hair, and there was no evidence of recession. The thyroid was not palpable. The penis was infantile, being 1¼ in. long. The scrotum contained only few rugae. Both testes measured 1 by 1 by 2 cm. and were located in the inguinal canal. The prostate was small. The blood pressure was 80 mm. of mercury systolic and 60 diastolic.

*Previously reported.[5]

Laboratory data—Roentgenographic examination showed the bone age to be 13 years, the epiphyses open in the lower extremities, and the sella turcica normal. The fasting concentration of blood sugar was 53 mg. per 100 cc.; chloride, 98.2 mEq. per liter; potassium, 4.7 mEq. per liter. The basal metabolic rate was –4 per cent; cholesterol, 327 mg. per 100 cc. of plasma; protein-bound iodine, 3.2 μg. per 100 cc. The urinary hormone assays were 0 mg. of 17-ketosteroids, 0.31 mg. for corticosteroids, 0 for gonadotropin, and 0 for estrogen.

Special tests—The intramuscular administration of corticotropin for six days in a dose of 40 mg. daily resulted in stimulation of the adrenal cortices as evidenced by the increased values for 17-ketosteroids and corticosteroids. Thyrotropin was administered intramuscularly, 30 mg. daily for five days. The radioiodine tracer studies revealed that the thyroid function was readily increased by the thyrotropin. Both these tests are confirmatory evidence that the primary deficiency was in the pituitary rather than in the end organs.

Testicular biopsy—The tubules were small and corresponded to those of a six year old child. The tubular wall was thin. A few spermatogonia were present, but there was no spermatogenesis. No Sertoli cells were recognizable. Interstitial tissue contained undifferentiated cells and no mature Leydig cells were seen. In general, the picture was that of an extremely immature testis without signs of stimulation by either endogenous or exogenous gonadotropin.

Comment—The history and findings in this case are fairly representative of patients with pituitary dwarfism. In reviewing the records of 12 such patients they were quite similar in most respects. The defect in pituitary dwarfism seems to be an intrinsic lack of development of pituitary function occurring early in life. It also may result from neoplastic involvement of the pituitary in childhood. In these patients there is a deficiency not only of gonadotropic hormones but also of growth hormone, adrenotropin, thyrotropin and other hormones which may be lacking in varying degrees and combinations.

Case Report—Adult Seminiferous Tubular Failure

History—A 30 year old man reported to the Mayo Clinic because of infertility. He had been married seven years, and his wife had not been pregnant. Five years prior to our examination he had been found to have no spermatozoa. Various types of treatment, including desiccated thyroid, testosterone, chorionic gonadotropin, and so forth, had been used. At the time of some semen examinations he had been found to have a few spermatozoa. He had normal libido and potentia. At the age of 10 or 11 years he had had mumps but did not recall having any pain or swelling of the testes. His development at the time of puberty had been normal, and he shaved daily. The results of his wife's investigation for infertility had been negative.

Examination—His height was 70 in. and his proportions were those of a normal male. He had a deep male voice, and his facial, axillary, body and pubic hair was normal. The penis was normal, and the testes were of normal size and consistency. The results of examination of the prostate were negative and revealed no prostatitis.

Laboratory data—The results of routine examinations, including urinalysis, hemoglobin, leukocyte count and roentgenograms of the chest, were negative or normal. Urinary 17-ketosteroids were 15.6 mg. In one semen examination there were too few spermatozoa to make an accurate count and in two others there were 9,000,000 and 11,000,000 per cubic centimeter. Motility was present. The basal metabolic rate was –16 per cent.

Testicular biopsy—The Leydig cells were normal. The tubules were of adult proportions with moderately thick walls. Spermatogenesis was proceeding, mainly through the spermatocyte stage. Only a few sperm were recognized. Most tubules contained sloughs of secondary spermatocytes and spermatids.

Comment—This patient is fairly representative of a large group who are investigated for infertility. Infertility is the commonest type of hypogonadism. As is so frequently the case, this man had some abnormality of the

seminiferous tubules, but on both physical examination and testicular biopsy there was good evidence of adequate Leydig cell function. There may be many causes for decrease or lack of sperm formation, such as cryptorchism, mumps orchitis, irradiation, and tubular failure (the commonest of the causes) of undetermined origin.

Case Report—Klinefelter's Syndrome

History—A 37 year old man reported to the clinic because of a recurrent ulcer on his left inner malleolus. Because atrophic testes were noted, the history concerning this was obtained. The patient thought his voice changed at age 12 or 14 years. He did not start shaving until the age of 32 years and at the time of his examination shaved every three to four days. He had experienced mild sexual urge but no nocturnal emissions. He had successful coitus once weekly after his marriage in 1952. He had not been aware of any abnormality of the testes. There was no history of illness except pneumonia as a child and asthma since childhood.

Examination—There was a stasis ulcer on the left inner malleolus 3 cm. in diameter due to chronic venous insufficiency. The patient had a boyish appearance, younger than his stated age. His voice, although masculine, was slightly high-pitched. His height was 74 in. and span 78 in. The distance from pubis to heel was greater than that from pubis to vertex. His weight was 176 lb., and blood pressure 120 systolic, 68 diastolic. The chin and cheeks were smooth with light beard. Axillary hair was adequate but chest and body hair was scant. His pubic hair was of female distribution. The penis was essentially normal but the testes were very small, being 1 by 1.5 cm. The scrotum had rugae. He had no clinical signs of myxedema.

Laboratory data—Urinalysis, leukocyte count, differential count, fasting blood sugar, and serology for syphilis were all negative. The hemoglobin measured 11.9 gm. and erythrocytes numbered 4,050,000 per cubic millimeter of blood. The roentgenogram of the sella turcica was negative. The basal metabolic rate was –27 per cent; however, the protein-bound iodine was 5.2 μg. per 100 cc., well within the normal range. Assay for urinary 17-ketosteroids was 15.2 mg. per 24 hours and an excess amount of urinary gonadotropin was found.

Testicular biopsy—The testicular biopsy showed hyalinized tubules and scars of tubules. Masses of Leydig cells in adenoma formation, typical of Klinefelter's syndrome, were present.

Comment—Klinefelter's syndrome usually consists of azoospermia, small testes and elevated pituitary gonadotropin. There may be wide variation in the habitus, beard, hair, gonads and genitalia in this syndrome, depending on time of onset and degree of Leydig cell failure. The Leydig cells may continue to function for variable periods after the seminiferous tubules have become sclerosed. If or when androgen deficiency develops, replacement therapy with testosterone is instituted.

Treatment

Rather than attempt to outline the detailed program of treatment for each syndrome, we will discuss it on a more general basis.

The treatment for male infertility has, as a whole, been empiric, unscientific and frequently ineffective. Thyroid preparations, all types of vitamins, gonadotropins and testosterone have been used. It is difficult to evaluate the results of any therapy, since so frequently pregnancy of the patient's wife may occur without any treatment of the husband, after several years of barren marriage. With that in mind it is impossible to be certain that desiccated thyroid is of any value for infertility in patients with low basal metabolic rate in the absence of myxedema. Since no harm can be done, a trial with this medication can easily be carried out if the rate is definitely low. In general, the gonadotropin preparations cannot be expected to be beneficial in the usual types of infertility, since there is no lack of endogenous gonadotropin, and furthermore the defect in tubular failure seems to reside intrinsically within the testes.

Heller and associates,[13] Heckel and McDonald[14] and others have reported on the use of testosterone propionate in adult semi-

niferous-tubule failure. If given in adequate doses, this hormone results in suppression of spermatogenesis. In variable periods of time, from weeks to many months, after discontinuing the hormone there may be a "rebound" at which time the semen frequently reveals more normal spermatozoa and a greater number of them. Pregnancy has been reported in the wives of some of the men so treated. In properly selected cases, on the basis of biopsy of the testes, we have outlined treatment consisting of intramuscular administration of testosterone propionate, 50 mg. daily for 40 to 50 days. Although we have not as yet reviewed all these cases, our impression is that relatively few resulted in pregnancy.

One great service a physician can render is to separate the group of men who obviously cannot become fertile, regardless of treatment, and then convincingly and sympathetically inform them of such finding. They can then plan adoption if they so wish rather than continue to seek hopeless medical care. A testicular biopsy is the best means of evaluating the state of the germinal epithelium. If the tubules are fibrosed or for any other reason spermatogonia are not present, then one can hardly expect spermatogenesis.

The treatment for Leydig cell failure, if symptoms and signs warrant, consists of replacement therapy with one of the testosterone preparations. Since, at least at present, it is not practical as a continued form of therapy to administer the various tropic hormones to patients with panhypopituitarism, end-organ replacement therapy is also used in these patients. If on investigation there is evidence of secondary thyroid, adrenal and gonadal failure, then the therapeutic regimen includes all these respective hormones.

Testosterone can be administered in several ways, namely, orally, sublingually (or buccally) or parenterally. Methyl testosterone can be given by either the oral or sublingual (or buccal) route, but is believed to be more effective by the latter. Because it is a rather expensive drug, it should be used by the most efficient route. In our experience 10 mg. three times daily, sublingually, usually results in adequate androgen effect. Occasionally, larger amounts are needed. Not infrequently, less than the initial dose may be adequate for maintenance, this being determined by trial. The rare occurrence of jaundice in patients taking methyl testosterone must be kept in mind.

Testosterone propionate may be administered sublingually or parenterally. Escamilla and Gordan[15] reported that this preparation is less effective than methyl testosterone when used sublingually. When administered intramuscularly, 25 mg. three times weekly usually gives evidence of good androgenic effect. The maintenance dose may vary considerably but 25 mg. every five to seven days is usually adequate. Pellets for implantation and long-acting testosterone preparation for intramuscular injection are also available. We have not had personal experience with these.

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Rationale and Value of Tracheotomy in Severe Preeclampsia and Eclampsia

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THE dividing line between severe preeclampsia and eclampsia is very delicate. Just where severe preeclampsia ends and eclampsia begins has not been determined with certainty. Is deep coma with marked hypertension and albuminuria any less lethal than convulsions, hypertension and albuminuria? Should management of a patient with the former symptoms differ from that of a patient with the latter? My answer is decidedly *no*. Therefore any discussion of convulsive toxemia should include severe nonconvulsive toxemia. However, for purposes of record and conformity I will speak of eclampsia as exhibiting albuminuria, marked hypertension, edema, convulsions and sometimes coma. Cases manifesting the same symptoms *except convulsions* are classified as severe preeclampsia. Furthermore, no case in the series reported herein is considered one of convulsive toxemia (eclampsia) unless convulsions occurred while the patient was in the hospital.

The laity and the profession and its trained assistants may and do have different ideas as to what constitutes a convulsion; I wish to emphasize that in this series no patient with a history of convulsions but failing to exhibit this symptom in the hospital died. Had patients with a history of convulsions but not presenting this symptom while in the hospital been included in this series, the statistical results would be much improved.

Tracheotomy

Since 1949 tracheotomy has been rediscovered, and the procedure is now utilized in a number of conditions where management previously was restricted to a medical regimen.

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(Since July 1, 1948, the Department of Obstetrics and Gynecology, Tulane University, has been responsible for the Obstetric and Gynecologic Service at Huey P. Long Charity Hospital, Pineville, Louisiana, as a "farming-out" project. Senior residents from the Tulane Unit, Charity Hospital, are rotated through the Huey P. Long Hospital and are in complete charge of the Division of Obstetrics and Gynecology, aided by weekly consultation visits by members of the Department of Obstetrics and Gynecology, Tulane University.)

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The value of tracheotomy as an adjunctive measure has been demonstrated in cases of poliomyelitis,[1,2] tetanus,[3] brain tumor,[4-7] cerebral abscess,[8] multiple rib fractures,[9] crushing injuries of the chest,[10] and a variety of medical and surgical conditions.[11,12] Thus its value has been proved in conditions where coma, obstruction of the tracheobronchial tree, or interference with respiration due to pain or paralysis exists. In three previous reports[13-15] my associates and I emphasized the results obtained when tracheotomy was used as an adjunctive method in treating severe preeclampsia or eclampsia. Our experience utilizing tracheotomy in 27 cases of convulsive toxemia and six cases of severe preeclampsia forms the basis of this report.

Altered Physiology in Tracheobronchial Obstruction

Carter and Giuseffi[10] believe that "in the normal subject with a tidal air of 500 cc. or more, the presence of a dead space of roughly 150 cc. is tolerated without difficulty. This dead space in no way contributes to ultimate oxygenation, and represents unnecessary work. Therefore, in patients able to ventilate only with abnormally reduced tidal air, this constant dead space becomes more and more detrimental to the efficiency of the impaired ventilatory act." Dead space involved consists of nasal passages, mouth, pharynx, trachea and tracheobronchial tree. Carter and Giuseffi, from experiments performed on autopsy specimens, concluded that when air enters the trachea just above the suprasternal notch, as contrasted to its entrance through the nose and mouth, the dead space is reduced approximately 100 cc., and "the more effective utilization of a tidal air which is reduced to levels incompatible with adequate ventilation by diminishing the volume of dead space appeals to the authors as an important physiologic effect of tracheotomy."

It is estimated that three-fourths of the resistance to breathing is located in the upper air passages. Resistance to breathing is increased when there is obstruction of the tracheobronchial tree, especially where there are secretory obstruction and failure of the cough mechanism. The cough mechanism normally clears the respiratory tract of accumulated secretions. When cough reflex is depressed or abolished as a result of coma, general debility, depression of the respiratory center, anesthesia or analgesia, or from any other cause, pooling of secretions in the nasopharynx may produce almost complete obstruction and the patient may drown in her own secretions. Laryngospasm may complicate the picture. With tracheotomy there is marked reduction in resistance to breathing, the obstructing pool of secretion is bypassed, and laryngospasm is no problem.

As a result of hypoxia or anoxia there are increased capillary permeability, pulmonary and cerebral edema, and damage of cardiac and nerve tissue. Only three to eight minutes of anoxia may result in damage or necrosis of brain cells. In cases of cardiac arrest at the time of surgery or delivery, assuring a clear airway and administering oxygen are the first steps in therapy—even before attempting to stimulate the heart. In patients whose heart action has been restored but in whom the interval of anoxia is prolonged, convulsions may be manifest in the recovery phase.

Von Leden[16] recently published an excellent article, with an extended bibliography, describing the advantages of tracheotomy in different conditions where obstruction of the tracheobronchial tree is a problem. In discussing tracheobronchial obstruction he stated: "Carbon dioxide, because of its greater molecular weight, diffuses even less than oxygen and is thus retained in the blood. This hypercapnia has not received due attention in the past; yet my own experience and that of my associates fully supports the theory that the effects of hypercapnia are even more disastrous than those of anoxia. Hypercapnia produces headache, restlessness, apprehension, disorientation and uncooperativeness in its early stages, while high concentrations induce narcosis, anesthesia, respiratory depression and circulatory collapse."

Von Leden believes that, though oxygen saturation might be satisfactory in the presence of respiratory obstruction, *hypercapnia* may reach dangerous proportions. His opin-

ion is shared by Plum and Wolff[17] and Blalock.[18] Hypoxia and hypercapnia in respiratory obstruction produce respiratory acidosis. Interference with normal gaseous exchange causes retention of carbon dioxide in the blood as free carbonic acid (respiratory acidemia), while hypoxia or anoxia results in excess lactic acid in the tissues with accumulation in the blood (metabolic acidosis). In eclampsia and severe preeclampsia, due to depressed renal function, renal acidosis develops. Therefore in severe preeclampsia or eclampsia three causes of acidemia may be present: (1) respiratory acidemia due to obstruction of the tracheobronchial tree by secretions or depressed respiration due to sedation, or coma; (2) metabolic acidemia due to hypoxia; (3) renal acidemia due to depressed renal function.

The pH of the blood is lowered and may hasten the onset of coma. According to von Leden, administering oxygen in the presence of hypoventilation is of no appreciable value in reversing hypercapnia and acidemia, and "the only treatment providing any real hope of success consists in removal of the obstructing secretion from the respiratory passages and re-establishment of normal alveolar ventilation."

In coma, in addition to accumulated tracheobronchial secretion, there is the problem of nasopharyngeal and salivary secretions. The latter alone may be in the range of 1000 to 1500 cc. daily.

It is evident, therefore, that in obstruction of the tracheobronchial tree there are reduced tidal air, increased resistance to breathing, hypoxia and anoxia, increased capillary permeability, pulmonary and perhaps cerebral edema, potential damage to nerve and cardiac cells, hypercapnia, and respiratory as well as metabolic acidemia. Thus, many vicious circles are established:

1. Anoxemia increases capillary permeability, producing edema which in turn increases the anoxemia.

2. Asphyxia produces depression of the respiratory center, resulting in decreased respiratory efforts which in turn accentuate the asphyxia.

3. Respiratory obstruction causes increased venous intrathoracic pressure, resulting in increased intracranial venous pressure, producing edema and depression of the central nervous system which further augment the obstruction.

4. Tracheal obstruction increases venous congestion, which increases cardiac load, which may eventuate in cardiac decompensation and further venous congestion.

Treatment of Eclampsia

As long as the etiology of eclampsia remains unknown, the treatment must, of necessity, be symptomatic. Many therapeutic agents have been advocated, tried, abandoned, repopularized or used continually. Each section of the country or each medical center has its own therapeutic regimen. Therapy in some institutions is only slightly dissimilar, whereas in others it varies greatly. In this presentation, the various therapeutic agents are not evaluated. I merely wish to present the program in vogue on the Tulane Unit, Charity Hospital, and evaluate the results. Needless to say, no *one* agent is specific, and treatment remains symptomatic.

Management of convulsive toxemia on our service has changed little since January 1, 1946, except for the recent introduction of tracheotomy. Tracheotomy was first performed on our service November 25, 1950. Since then it has been used with excellent results in cases in which it was deemed necessary. In brief, the program for management of convulsive toxemia in effect since January 1, 1946 consists of sedation with morphine sulfate, SODIUM AMYTAL®, DEMEROL® or phenobarbital, alone or in combination. Magnesium sulfate is used in many instances. The quantity of fluids administered varies, neither hydration nor dehydration being the goal. Rather, fluid administration is comparable to that in the regimen used by us in treating lower nephron nephrosis, namely, 1000 to 1500 cc. of 5 per cent glucose, sufficient to compensate for the insensible loss, plus an added quantity equal to the urinary output each 24 hours.

In addition to these measures aimed at controlling convulsions, lowering blood pres-

sure, and maintaining fluid balance, attempts to assure an adequate airway are important.

Rationale of Tracheotomy in Eclampsia

Many factors enter into the problem of respiratory distress and oxygenation in the eclamptic patient. Marked depression of the respiratory rate can occur as a result of the amount of sedation needed to control convulsive seizures. Edema of the lung sometimes results from abnormal retention of fluids or from heart failure. Laryngospasm, either occurring spontaneously or induced by the attempted passage of an airway, is not infrequently encountered. Accumulation of secretions in the tracheobronchial tree produces respiratory obstruction, which results in the altered physiology already discussed. Occasionally, exhaustion of the patient resulting from violent respiratory efforts has necessitated artificial respiration for varying periods. Respiratory distress and hypoxia were so marked in some instances that the patients were cyanotic.

Relief from respiratory distress may be obtained in many cases by the use of metal or rubber airways with repeated aspiration of secretion from the pharynx, larynx and trachea. In addition, administration of oxygen by mouth or nasal catheters is beneficial.

Brown[19] believes that secretions become less tenacious if oxygen is allowed to pass through alcohol before entering the mouth or catheter. Reich and associates[20] recommend bubbling oxygen through 2-ethyl hexanol which produces results superior to either 95 per cent or 50 per cent ethyl alcohol. We have not had any experience with these methods.

Rubber or metal airways together with suction and oxygen do not always produce the desired results. Furthermore, if left in place for more than a short period, a large endotracheal tube may damage the pharynx or larynx, and aspiration through such a tube requires expert attendance. Obviously, bronchoscopic inspection and aspiration have no place in the treatment of the critically ill patient where frequent repeated aspirations are needed. Therefore, it has been our policy since November 1950 to employ tracheotomy in cases of eclampsia in which laryngospasm or severe obstruction to the tracheobronchial tree is present and repeated aspiration will be needed to keep an airway effective. Earlier in our experience, tracheotomy was performed only if an airway and repeated suction failed. However, failure of airways and suction to relieve the obstruction in five cases observed in 1951 and the dramatic results obtained by subsequent tracheotomy in these patients led us to decide that where a long-term airway and suction would be needed, tracheotomy was indicated.

Cerebral hemorrhage, cerebral softening or meningeal hemorrhage can occur in eclampsia. Sheehan[21] found such lesions in 24 of 67 true eclamptic patients who had more than one convulsion and in 14 of 31 preeclamptic patients who died in coma with no convulsions or only a single convulsion. It is estimated that cerebral hemorrhage develops in no more than 3 per cent of all cases of eclampsia.[22] Utilization of tracheotomy in cases of severe head injuries with coma and respiratory difficulty has given excellent results.[4]

Tracheotomy therefore might help in cases of severe preeclampsia or eclampsia where cerebral lesions exist, for any measure of value when cerebral hemorrhage results from external trauma should benefit patients with cerebral hemorrhage from other causes. Proceeding on this premise, we decided to employ tracheotomy as adjunctive therapy for patients with eclampsia or severe preeclampsia who had marked respiratory difficulty and failed to respond to more simple methods, who gave evidence of a cerebrovascular accident, or who demonstrated severe coma.

Tracheotomy allows instant and repeated aspiration of the tracheobronchial tree as well as administration of oxygen. The pool of secretions in the hypopharynx is bypassed, and the not uncommon complication of aspiration pneumonia is minimized.

Observations and Results

From January 1, 1946 to July 1, 1954, 123 consecutive patients with convulsive toxemia (eclampsia) were admitted to the Tulane

TABLE 1

CONDITIONS IN WHICH TRACHEOTOMY WAS PERFORMED, TULANE UNIT, CHARITY HOSPITAL, NEW ORLEANS
(November 25, 1950 to July 1, 1954)

	NUMBER OF CASES
Convulsive toxemia (eclampsia)	27
(Ante partum, 23; post partum, 4)	
Nonconvulsive toxemia	6
	33

TABLE 2

PRINCIPAL INDICATIONS FOR TRACHEOTOMY

	NUMBER OF CASES
Labored respiration	21
Laryngospasm	7
Respiratory rate less than 10 per minute	1
Respiratory rate less than 5 per minute	3
No respiration on admission	1
	33

Unit, Charity Hospital, and the Huey P. Long Charity Hospital and managed by the staff, residents and fellows of the Department of Obstetrics and Gynecology, Tulane University. As previously stated, tracheotomy was first used on our service in November 1950; thus we may divide this series into the pre-tracheotomy and post-tracheotomy eras. Tracheotomy was performed in 27 cases of convulsive toxemia. In addition it was utilized in six cases of nonconvulsive toxemia in which the patients were in coma or had marked respiratory distress, or both.

In table 1 the types of disease for which tracheotomy was employed are listed. In the majority of cases it was performed for antepartum eclampsia. The principal indications for its utilization are listed in table 2. Only the principal indication is noted for each case. In many cases, more than one of the indications tabulated were present.

It is to be emphasized that although the principal indications for tracheotomy are listed in table 2, all patients had marked respiratory difficulty and greatly increased tracheobronchial secretions. In one case, respirations had ceased entirely on admittance but were resumed promptly following tracheotomy and artificial respiration. Some patients were cyanotic prior to tracheotomy. In all cases tracheotomy was followed by immediate improvement in respiration. In addition, it is the impression of our residents, fellows and staff that, *following tracheotomy, less of the hypnotic drugs are required for adequate sedation than before tracheotomy or where tracheotomy was not utilized.* The patients with eclampsia ranged in age from 16 to 36 years (table 3).

The interval between admission of the patient and performance of tracheotomy is extremely important (table 4). In one of the two cases in which death occurred, tracheotomy was not done until the patient was moribund. As experience is gained in the use of tracheotomy and the marked improvement following tracheotomy is noted, one employs it earlier and with greater frequency.

Type of delivery and time of delivery as related to tracheotomy are listed in table 5. In four cases convulsions were postpartum in origin. Delivery was divided equally between the vaginal route and cesarean section. Of the 13 patients delivered by cesarean section, three had severe abruptio placentae as well as convulsive toxemia, three had nonconvulsive toxemia and were in severe coma with unripe cervices, and three had convulsive toxemia with long, rigid, undilated cervices.

Of the patients having cesarean section as well as tracheotomy, one died on the twenty-fifth postpartum day. An abstract of her history is presented later.

Anesthesia for delivery following tracheotomy (table 6) did not present any problem. In all cases the tracheotomy tube was removed by the tenth post-tracheotomy day. In the majority the tube was removed on the fifth day. There were no instances of complications or post-tracheotomy aphasia. In no case was hospitalization extended because of tracheotomy (table 7). In 13 cases, respiratory symptoms were so severe the tracheotomy was performed within one hour of admission to the hospital. The longest interval from admission to tracheotomy was 48 hours (table 4).

TABLE 3

AGES OF PATIENTS WITH ECLAMPSIA

GROUP	AGE (YEARS)				
	15-20	*20-25*	*25-30*	*30-35*	*35-40*
Convulsive toxemia	13	3	4	3	4
Nonconvulsive toxemia	3	0	0	3	0
TOTALS	16	3	4	6	4

TABLE 4

INTERVAL BETWEEN ADMISSION AND TRACHEOTOMY

GROUP	HOURS ELAPSED					
	0-1	*1-6*	*6-12*	*12-24*	*24-48*	*48+*
Convulsive toxemia	13	6	1	2	4	1
Nonconvulsive toxemia	0	0	2	3	1	0
TOTALS	13	6	3	5	5	1

TABLE 5

TYPE OF DELIVERY AND TIME OF DELIVERY AS RELATED TO TRACHEOTOMY

GROUP	VAGINAL DELIVERY		CESAREAN SECTION	
	Pretracheotomy	*Post-tracheotomy*	*Pretracheotomy*	*Post-tracheotomy*
Convulsive toxemia	4	15	0	9
Nonconvulsive toxemia	0	1	0	4
TOTALS	4	16	0	13

Deaths

Case 1—A 20 year old Negro woman, gravida 1, about 38 weeks pregnant, was admitted with coma, convulsions, laryngospasm, hypertension, albuminuria, edema and coarse rales throughout both lung fields. Fetal heart tones were not heard, and definite evidence of a dead fetus and abruptio placentae was present. Sedatives were given but did not improve the respiratory difficulty. Tracheotomy was performed 45 minutes after admission. Respiration improved immediately. The following day the patient's condition was generally improved but evidence of increasing severity of signs and symptoms of premature separation of the placenta necessitated cesarean section under general anesthesia. A severe Couvelaire uterus was encountered which would not contract following removal of the fetus. Therefore cesarean hysterectomy was performed. One unit of fibrinogen was administered immediately to correct the constant ooze from the wound edges. Following its administration, the oozing stopped.

The tracheotomy tube was removed on the tenth postpartum day. On the twelfth postoperative day, because of serosanguineous drainage from the wound, the patient was taken to the operating room and the wound examined under general anesthesia. It was found that the fascia had separated but the peritoneum was intact. Secondary closure of the wound was performed. From then on recovery was steady.

The patient was ambulatory on the twenty-first postoperative day. A mild generalized convulsion followed by jacksonian type convulsions developed. During the entire postpartum course the blood pressure varied between 142/80 and 184/118. On the twenty-fifth postoperative day she had a generalized convulsion. Reconsultation with the depart-

TABLE 6

POST-TRACHEOTOMY ANESTHESIA FOR DELIVERY

TYPE OF DELIVERY	ANESTHESIA			
	None	*Local*	*Gas-oxygen*	*Spinal*
Vaginal	7	8	1	0
Cesarean section	0	9	3	1
TOTALS	7	17	4	1

ments of medicine and neurosurgery led to the diagnosis of hypertensive encephalopathy. Lumbar puncture showed clear fluid at a pressure of 330 mm. of water. There was no respiratory difficulty from the time the tracheotomy tube was removed until the series of convulsions on the twenty-fifth postpartum day, at which time the patient died. Permission for autopsy was not granted.

Case 2—A 21 year old primigravida was admitted to the Huey P. Long Charity Hospital at Pineville, Louisiana on June 14, 1951. She was approximately 28 weeks pregnant and had hypertension, edema, proteinuria, coma and convulsions. Rales were found in both lung fields. Sedatives, nasal oxygen, intravenous fluids and digitalis were administered. Twenty-four hours later the patient was in poor condition, the blood pressure was 118/60, she remained in coma, and marked respiratory difficulty developed. Tracheotomy was performed and respiration improved, but the patient died a few hours later. Autopsy disclosed marked edema of the brain but no softening or hemorrhage.

Tracheotomy was of benefit in the acute phase of the illness in case 1, the patient dying 13 days following removal of the tracheotomy tube and apparent recovery. In the light of added experience, I believe that tracheotomy should have been performed earlier in the latter case, admitting that it is a matter of conjecture whether or not the ultimate result would have been different.

Results of treatment of convulsive toxemia are summarized in table 8.

Summary and Conclusions

Many and varied problems are encountered in the management of eclampsia and severe preeclampsia. Therapy in eclampsia is as varied as are the theories of its origin. As yet, a specific single therapeutic agent has not been introduced that produces excellent results in all cases.

On the Tulane Unit, Charity Hospital, hypertension is combated by bed rest and sedation. Morphine sulfate is the sheet anchor of our therapeutic regimen in this respect. Though we know that vasospasm plays a large part in producing hypertension, we have not yet employed any of the hypotensive agents. When hypertension cannot be controlled by bed rest and morphine sulfate, the pregnancy is terminated.

Convulsions are controlled by the use of morphine sulfate aided by small doses of phenobarbital. If this does not suffice, other barbiturates such as Sodium Amytal are given. Patients with convulsions must be "splinted where they lie." Every physician does not have hypotensive agents in his bag but nearly all have morphine sulfate. It should be given intravenously, as its administration by any other route might result in delay of absorption due to edema present in the body tissues. Whether one uses magnesium sulfate is of no import. Furthermore, administration of hypotensive drugs must be carefully controlled, as too se-

TABLE 7

LENGTH OF HOSPITALIZATION AND DAY ON WHICH TRACHEOTOMY TUBE WAS REMOVED

	DAYS				
	2-5	*5-10*	*10-15*	*15-20*	*20+*
Tracheotomy tube removed	20	13	0	0	0
Hospitalized post partum	1	10	14	3	5

TABLE 8

RESULTS OF TRACHEOTOMY FOR CONVULSIVE TOXEMIA

PERIOD	NUMBER OF CASES	TRACHEOTOMY PERFORMED	PATIENTS SURVIVED	PATIENTS DIED	
				Number	*Per Cent*
1/1/46 to 11/1/50	62	0	57	5	8
11/1/50 to 7/1/54	61	27	59	2	3.2
TOTALS	123	27	116	7	5.6

vere a drop in blood pressure is undesirable. Conversely, so much sedation is required at times to control convulsions that respirations are depressed.

We do not employ digitalis or phlebotomy in the therapy of eclampsia. Cardiac and lung manifestations are usually due to hypoxia and hypercapnia and not to cardiac failure. Tracheotomy is more valuable in combating signs and symptoms of cardiac failure or respiratory difficulty than is any other agent or agents.

Oliguria and anuria are treated as one would treat a case of lower nephron nephrosis. Fluid balance should be so regulated that the patient receives 1000 cc. of 5 per cent glucose in distilled water daily to make up for insensible loss of fluids. An amount of the same solution equal to the 24 hour urinary output should be added daily. We do not believe that a damaged kidney can be made to work more effectively by overloading patients with fluids or increasing the concentration of the glucose in the infused material.

Previous studies of eclampsia have emphasized pathology and altered physiology in the liver, kidneys, brain, heart and blood vessels. We have produced evidence that altered physiology in respiration as a result of cerebral hemorrhage, sedation, coma or tracheobronchial obstruction plays an important role in the clinical manifestations of the disease. The lung is as important as any other organ when eclampsia or severe preeclampsia is encountered. Respiratory distress is often encountered in our eclamptic patients. Of the five patients who died in the pretracheotomy era, four did so within 24 hours of admission. The others died four days after entry but all five had *marked respiratory distress.*

As a result of our experience and that of others,[23-25] I believe that tracheotomy has a definite place as an adjunctive measure in the therapy of eclampsia.

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Cervical Disk, Shoulder–Arm–Hand Syndrome

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PAIN in the shoulder, arm, hand and neck is a common syndrome that may be caused by many underlying conditions. The age of the patient, the nature of the pain and the occurrence of trauma to the shoulder and neck may indicate the cause and treatment. Because of the many factors involved in pain of this type, careful history and examination are necessary. This type of pain frequently is relieved by conservative treatment; however, in view of the fact that a protruded intervertebral disk in the cervical region or some other intraspinal lesion may play a part in producing such pain, these factors should be kept in mind.

Askey,[1] in 1941, first introduced the term "shoulder-hand syndrome." This entity was presumed to occur on a reflex dystrophic basis and interest was renewed in the reflex dystrophies, with the appearance of a number of articles dealing with phases of reflex sympathetic dystrophy of the upper extremities. Numerous classifications and symptom complexes were submitted; as with any new and imperfectly understood syndrome, there was a tendency to divide and subdivide, and to describe each new facet of the syndrome and then apply a synonym. Perhaps the main cause of the confusion concerning this syndrome is an inability to appreciate the basic neurophysiologic processes involved and to realize that primary stimuli from such unrelated structures as the gallbladder, heart, lungs, cervical vertebrae, spinal cord and even the cerebral cortex can produce similar reflex sympathetic dystrophic disturbances in the upper extremity.

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Clinical Aspects

The shoulder-hand syndrome may follow any condition that produces pain in the shoulder, for it is the pain that initiates the chain of events making up this syndrome. In the previously mentioned report by Askey,[1] the shoulder pain was attributed to coronary occlusion. Just as likely, it might follow tears in the rotator cuff of the shoulder, fracture of the humerus with prolonged immobilization, intramedullary tumors of the spinal cord, protruded cervical intervertebral disks, disease

of the gallbladder, or periarteritis nodosa. The first prerequisite is pain in the shoulder, regardless of its cause. Stiffness of the shoulder develops later. This may occur at the onset of pain or it may follow pain after varying periods. The major cause of this stiffness appears to be disuse. The patient tends to avoid any motion of the joint to prevent the occurrence or intensification of pain. Disuse and stiffness in turn lead to more pain that further intensifies the disuse.

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Not all patients who have pain in the shoulder undergo dystrophic changes in the hand on the affected side. Indeed, by far the majority recover completely. Others experience pain and stiffness and then recover. Some people exhibit a low threshold of tolerance to pain and have a strong tendency to avoid motion in a painful shoulder. They tend to hold the joint immobile, and efforts to encourage them to begin motion to prevent more serious changes are met with apathy and even resistance. A number of reports have emphasized the importance of such personality factors in the production of this syndrome; these factors have been variously denoted by such terms as "neurotic personality," "psychically deviated" and "periarthritic personality."

After the onset of pain and stiffness, there may be a latent period of days to months before vasomotor and trophic changes appear in the hand. At first these changes are mild, consisting of painful swelling involving the entire hand, with stiffness of the skin and loss of the normal cutaneous wrinkles. Vasodilatation usually is present in this early phase, with increased surface temperature and sweating. If the process goes unchecked, vasodilatation gradually disappears, the hand becomes pale and dry, sometimes cyanotic, the skin is stretched taut, and trophic changes appear. In the final stages the small muscles of the hand become atrophied, and deformities and Dupuytrenlike contractures appear. This is the chain of events making up the shoulder-hand syndrome if one could follow a case from beginning to end. The changes seen at various stages of the syndrome differ greatly, and the incautious observer might consider different stages as separate entities, failing to appreciate that these changes appear to be part of the same neurophysiologic process.

Mechanism

The neurophysiologic mechanism currently accepted as being involved in the production of this syndrome is depicted in figure 1. To de Takats,[2,3] Lorente de Nó,[4] Livingston[5] and Steinbrocker,[6] with their various associates, must go the credit for working out the pieces of the puzzle that fit together to make up the present-day concept of this mechanism. As used here, the term primary disorder refers to any of the myriad conditions able to produce shoulder pain. These will be discussed later.

In a consideration of what is capable of producing the initial pain in the shoulder, it is important to keep in mind the concept of intrasegmental diffusion of pain within the spinal cord. The pain may originate in the shoulder itself, as from a fracture of the humerus, tendinitis, a tear in the supraspinatus tendon or rheumatoid arthritis. The pain may be referred to the shoulder from some distant structure, such as the pain felt along the upper border of the trapezius muscle and into the tip of the shoulder that is noted so commonly in irritative lesions of the diaphragm. This pain is felt in the shoulder because the sensory supply to both the diaphragm and this portion of the shoulder is derived from the fourth segment of the cervical portion of the spinal cord; thus, the impulses coming into this segment from the diaphragm are interpreted by the body as pain in the shoulder as the impulses diffuse intrasegmentally in the fourth cervical segment.

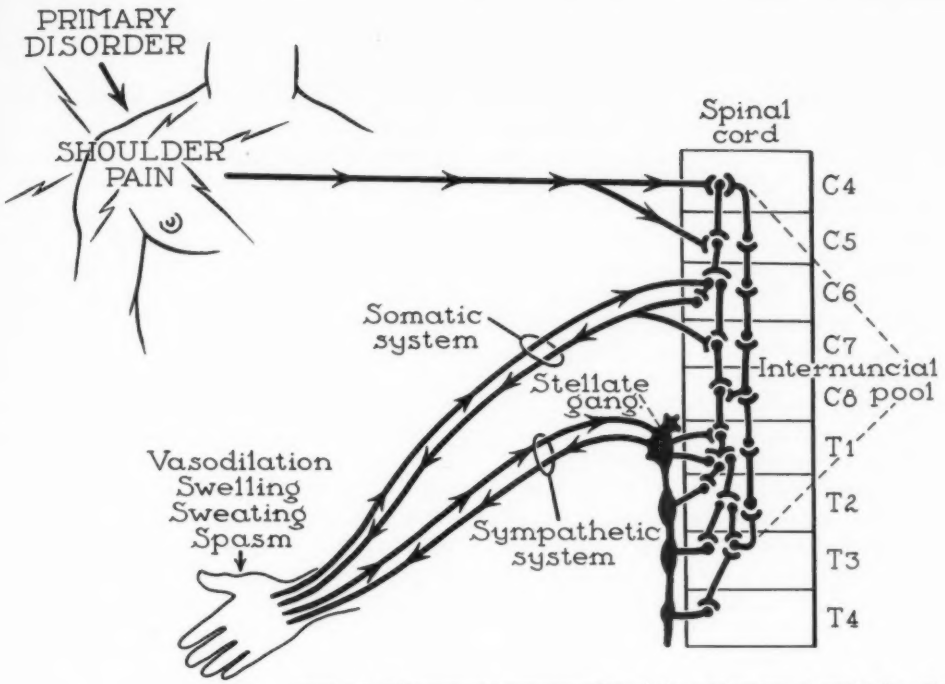

FIGURE 1. Diagrammatic representation of the mechanism of production of the shoulder-arm-hand syndrome.

Another example is cardiac (anginal) pain referred to the shoulder and inner aspect of the arm and forearm. As pointed out by Miller,[7] the primary afferent pathways from the heart enter the first, second, third and fourth thoracic segments of the spinal cord over the cardiac nerves, but afferent impulses also are probably carried over accessory sympathetic fibers to enter the spinal cord in the cervical segments. These fibers entering the spinal cord in the segments that innervate the shoulder, namely C4, C5 and C6, bring about intrasegmental diffusion of the impulses so that pain is felt in the shoulder and arm. Therefore, the patient experiences pain in the shoulder whether the fourth, fifth and sixth cervical segments receive impulses from the shoulder itself or whether these segments are excited by impulses coming from some other structure receiving its innervation from these same segments.

Referred pain, then, is an example of intrasegmental diffusion of pain. However, the changes seen in the hand in this syndrome are not a manifestation of this intrasegmental diffusion of pain, because the entire innervation of the hand is derived from several segments of the spinal cord. Not only does the hand receive somatic innervation from C6, C7 and C8 but the sympathetic supply to the blood vessels in the hand, as well as in the arm, is derived from cell bodies situated in the first through the fourth thoracic segments of the spinal cord.

How do the initial impulses entering the cord in the fourth through the sixth cervical segments ultimately bring about excitation of cell bodies situated in the lower cervical and upper thoracic segments? In 1938, Lorente de Nó[4] pointed out the existence of a series of neurons in the gray matter of the spinal cord that are capable of spreading an impulse over several segments of the spinal cord. This network is termed the internuncial pool. Since these neurons communicate with one another, they are also capable of re-exciting one another to bring about a prolonged effect.

Thus the impulses initiated by the primary disorder enter the fifth cervical segment and are spread over the lower cervical and upper

thoracic segments via the internuncial pool to excite the motor efferent systems, both somatic and sympathetic. The impulses reaching the efferent somatic system are carried over the cervical roots to the brachial plexus and then via the peripheral nerves to bring about muscular spasm in the hand. The sympathetic impulses reach the hand over more than one route, an important consideration in treatment and its evaluation. These sympathetic impulses may leave the spinal cord via the ventral roots, pass through the paravertebral ganglion and chain and then through the stellate ganglion to reach the hand perivascularly or along peripheral nerves.

In addition, sympathetic impulses apparently may ascend within the cord in the gelatinous substance of Rolando and ultimately pass out of the spinal cord over the anterior roots in the cervical region and thence to the brachial plexus and peripheral nerves to reach the hand. The important difference is that some sympathetic fibers apparently do not pass through the paravertebral sympathetic chain.

Thus, overstimulation and overaction of both somatic and sympathetic motor systems bring about the changes seen in the shoulder-hand syndrome. As already indicated, first there are vasodilatation, swelling and muscular spasm. These in turn give rise to new afferent pain impulses that reach the spinal cord over both somatic and sympathetic afferent systems. These impulses coming into the cord further excite the internuncial pool and bring about more overaction of the sympathetic system that in turn causes more pain, thus establishing the concept of the vicious circle. The initial pain in the shoulder in some people sets off this vicious circle; the latter, when allowed to operate unhindered for a sufficient period, is capable of self-perpetuation and is capable of re-exciting itself to produce more stiffness and pain and more severe pathologic changes in the hand, even though the initial pain caused by the primary disorder is removed.

Etiology

As stated previously, there are many causes of pain in the shoulder. To review them all would take more space than is available. Those interested in an extensive classification of such factors are referred to the article by Coventry.[8]

The best way to ascertain the cause of pain in the shoulder is by means of a carefully taken history. If the cause of the pain is not suggested by the history, the most logical place to seek the cause is in the local region about the shoulder.

Local causes. Lesions of the rotator cuff—Lesions of the rotator cuff are probably the commonest cause of painful shoulder (figure 2). The tendons of the supraspinatus, infraspinatus, teres minor, and subscapularis muscles join as a common tendon as they are attached to the greater tuberosity of the humerus, and it is this combined tendon that is called the rotator cuff. The lesions in question, such as partial tears of the supraspinatus tendon, calcareous deposits and complete tears of the cuff, are mainly the result of degeneration, with the added factor of acute injury. In youth, it is almost impossible to tear the cuff; instead, the cuff will partially or completely avulse the bony tuberosity. The process of degeneration goes on gradually through the years and may represent the results of such factors as repeated minor trauma, poor posture and daily strain to the shoulders in strenuous occupations.

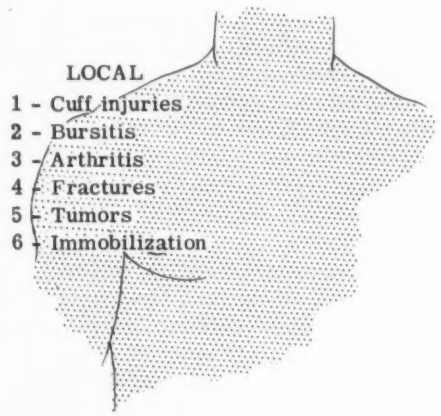

FIGURE 2. Local conditions producing pain about the shoulder and arm.

These lesions are seen most commonly in persons who are more than 40 years of age. Although degeneration is the primary factor involved in producing such lesions, the patient frequently gives a history of a recent fall or severe strain to the shoulder followed by pain in the shoulder and inability to perform full abduction of the arm. Since the pain is severe, the patient most commonly consults a physician early. When patients in this age group give a history of injury, even though slight, followed by pain and inability to abduct the arm, and when roentgenologic examination shows no evidence of fracture or dislocation, the diagnosis of rupture of the rotator cuff can be made.

The rotator cuff is the most frequent site of calcium deposition in the locomotor system. The cause of the deposits is probably repeated minor trauma. Many persons have calcium in the cuff as shown roentgenologically but do not have symptoms; others have only occasional aches and pains in the shoulder after unusually strenuous activity. Still others give histories of some injury followed by acute, severe pain in the shoulder, with extension down the arm or into the scapular region. The arm is held fixed at the side, and attempts to abduct the arm cause excruciating pain.

Any pressure on the shoulder increases the pain and the patient is usually unable to sleep. In these instances, the trauma apparently brings about a change in the previously quiescent deposit of calcium. The deposit increases in size by taking up fluid, and as the surrounding region becomes greatly hyperemic the enlarging deposit involves the floor of the subacromial bursa and ruptures into it, giving rise to subacromial bursitis.

Most authors agree that it is doubtful if the bursa of the shoulder is ever primarily involved; instead, bursitis is a secondary manifestation of underlying pathologic changes in the rotator cuff. The subacromial bursa lies over the rotator or musculotendinous cuff, in intimate contact with it. Lesions of the cuff, tears, hematomas or deposits of calcium irritate the floor of the bursa, and bring about hyperemia and swelling of the bursa and clinical signs of acute bursitis. The lesion actually responsible for the irritation of the bursa may have been present for years, the acute symptoms being precipitated by some recent trauma, even though the latter may be minor.

Rheumatoid arthritis—Local manifestations of arthritis may involve the shoulder joint and cause considerable pain. However, recognition of the generalized disease, with destructive changes in other joints, leads to the correct diagnosis.

Immobilization—Restriction of movements of the shoulder owing to a variety of causes may lead to pain in the shoulder. Common examples are Colles' fractures, when the arm is kept for long periods in a sling, and fractures of the humerus and elbow. One also should keep the factor of immobilization in mind in hemiplegia, injuries to peripheral nerves with paralysis, in the use of dressings after removal of a breast when the arm is immobilized by incorporating it into the dressing, and in the treatment of injuries and fractures of the clavicle, when the arm is fixed by the dressing.

Fractures, dislocations and tumors—These entities need no further comment as they are adequately demonstrated in roentgenograms of the shoulder and as such are obvious causes of a painful shoulder.

Vertebral lesions (figure 3)—Fractures—Fractures following crushing, acute flexion and whiplash injuries can lead to localized pain in the neck, and are revealed by roentgenologic examination of the cervical portion of the spinal column. These lesions give rise to pain in the shoulder by bony impingement on one of the cervical nerve roots innervating the shoulder, and are frequently accompanied by evidence of injury to the spinal cord itself, such as anesthesia and paresis of varying degree or paraplegia or quadriplegia. The likelihood of production of the shoulder-hand syndrome is further enhanced by the frequent loss of motor power in the arm, which allows the factor of disuse to operate more readily.

Hypertrophic arthritis—Arthritis of the cervical portion of the spinal column is an extremely common condition in older patients. However, in cases in which roentgenologic examination reveals evidence of these changes, the patients do not have any symptoms, even

in the presence of advanced changes. Others may have pain localized to the region of the deltoid, scapular or pectoralis muscles. Usually, no history of acute injury can be obtained, but the patient notes insidious onset of pain and stiffness in the neck, with frequent episodes of stiffness, accompanied by pain in the shoulder, or in the shoulder, arm and hand.

Roentgenograms may reveal firm bony ridges on the posterior aspect of the vertebral body with formation of marginal spurs; three-quarter views may show narrowing of the intervertebral foramina due to hypertrophic changes. Results of neurologic examination may be normal, or there may be evidence of extensive involvement of a nerve root, with anesthetic zones and reflex changes with or without weakness in specific groups of muscles. Myelography performed by employing ethyl iodophenylundecylate (PANTOPAQUE®) may demonstrate the encroachment on the nerve root by revealing defects in the nerve sleeves.

Protruded intervertebral disks—Protrusion of an intervertebral disk in the cervical region occurs more commonly than most physicians realize; approximately 10 per cent of all protrusions of intervertebral disks occur in the cervical region. The most common sites of protrusion in this region are between the fifth and sixth and between the sixth and seventh cervical vertebrae; less common sites are between the fourth and fifth cervical and between the seventh cervical and first thoracic vertebrae. Protruded disks are extremely rare above the fourth cervical vertebra.

A disk may protrude in the midline, at the lateral aspect of the intervertebral space so as to impinge on the nerve root as it leaves the vertebral canal, or at the extreme lateral aspect of the space so that the nerve root is involved while it is in the intervertebral foramen. Protrusions in the midline usually give rise to involvement of the long tracts because of pressure exerted on the spinal cord itself. They produce signs such as a reduced sense of position in the lower extremities, Babinski's sign, and weakness and spasticity of the lower extremities.

The more common protrusion is lateral,

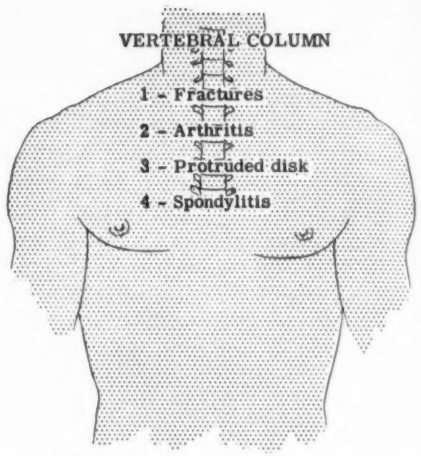

FIGURE 3. Vertebral lesions that may produce pain in the shoulder and arm.

with impingement of the nerve root as it enters the intervertebral foramen. This results in true radicular pain, namely, a sharp, lancinating, knifelike pain that begins in the back of the neck and shoulder and then extends down the arm and forearm to involve one or more fingers. This radicular pain is characteristically brought on or sharply increased by coughing, sneezing or straining at stool. The head may be held tilted to one side or the other, and motions of the neck are frequently reduced in all directions. Roentgenologic examination frequently reveals loss of the normal cervical lordosis, the neck being held straight. Most often, there is narrowing of the involved cervical interspace, and marginal spurs may be noted.

Results of neurologic examination vary with the root involved and the direction of the protrusion. As stated before, midline protrusions give rise to long-tract signs with or without radicular pain. If the sixth root is involved by a protrusion of the disk between the fifth and sixth cervical vertebrae, pain is present in the scapular region, with extension down the outer side of the arm, into the radial aspect of the forearm and into the thumb and index finger. There may be weakness of the biceps, with diminished or absent reflexes.

If the seventh root is involved between the

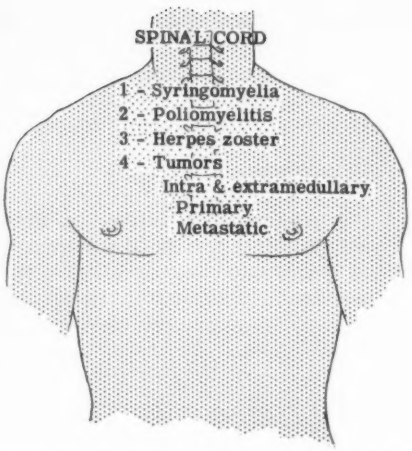

FIGURE 4. Lesions of the spinal cord that should be considered in the differential diagnosis of pain in the shoulder and arm.

sixth and seventh vertebrae, the pain extends from the neck and scapular region through the arm and forearm to end in the middle finger. In this case, there may be weakness of the triceps muscle, with diminution or absence of the triceps reflex. If the fifth root is involved, most of the pain and weakness is in the deltoid group of muscles, whereas involvement of the eighth root is accompanied by more weakness and wasting in the small muscles of the hand and the pain is more localized to the ulnar aspect of the hand. These patterns of pain are only general, and great variations may occur from case to case.

Rheumatoid spondylitis—This is a chronic, usually progressive disease involving the apophyseal joints of the spinal column, the paraspinous ligaments and the sacro-iliac joints. Whether this is an expression of rheumatoid arthritis in the spinal column or a separate entity remains disputed. Pain in the neck and shoulder may be a prominent feature as the cervical region of the spinal column becomes involved. The diagnosis is made by the history of long-standing pain in the lower part of the back, with early-morning jelling, the restricted thoracic expansion and the characteristic roentgenologic findings of sclerosis of the sacro-iliac joints with marginal demineralization, involvement of the apophyseal joints of the spinal column and calcification of the paraspinous ligaments.

Lesions of the spinal cord (figure 4)—Syringomyelia—This is not usually a painful disease; rather, it comes on insidiously, with wasting of the shoulder girdle and small muscles of the hand, and characteristic loss of pain and temperature of the jacket type of distribution. However, there may be a dull aching pain in the shoulders and thorax that is steady and may persist. This is thought to be a central type of pain.

Poliomyelitis—This need only be mentioned, for the diagnosis is usually not difficult. In the early acute stage, the severe pain is well known. Because certain muscles of the shoulder may be denervated, the shoulder becomes painful as disuse is manifested.

Herpes zoster—This properly may be considered with lesions of the spinal cord, as it is now believed that this inflammation of viral origin is not confined to the posterior root ganglion, as was formerly thought, but also involves the gray matter within the spinal cord. Pain and a vesicular type of eruption following the course of the involved nerve root are the characteristic features of this disease in the acute phase. Later, pigmentation and scarring reveal the previous acute attack. The pain may not disappear after the acute phase, but may persist in a severe steady form, the so-called postherpetic neuralgia. Unfortunately, it is extremely refractory to all types of treatment, both medical and surgical. This persistent pain may lead to immobility of the arm in an attempt to lessen the pain, with initiation of reflex sympathetic dystrophy.

Tumors—Neoplasms of the cervical region of the spinal cord frequently produce pain as their initial symptom. The pain may be dull and aching or sharp and knifelike; it may be the only symptom produced by the tumor for years, particularly in the case of extramedullary lesions. Although pain is a more frequent accompaniment of extramedullary than of intramedullary tumors, the latter also may produce intractable pain. This was vividly portrayed in the case of a 13 year old girl who gave a history of falling while roller skating about three months prior to her examination

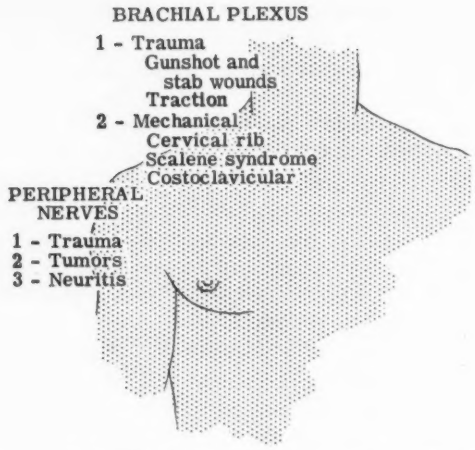

FIGURE 5. Lesions of the brachial plexus and peripheral nerves that may produce the syndrome.

at the Mayo Clinic. Subsequent to the fall, she had severe pain in the neck, shoulders and upper arms, making it difficult for her to use her arms. Her neck voluntarily was held virtually immobile. This condition persisted until she was brought to the clinic. At operation a huge intramedullary hemangio-endothelioma was found to involve the fifth, sixth and seventh cervical segments, yet her only symptom had been the afore-mentioned pain in the neck, shoulders and arms.

Pain produced by tumors of the spinal cord may be constant or intermittent. It frequently occurs at night after the patient has gone to sleep, and it awakens the patient and becomes so severe as to force the patient to arise and walk about in an attempt to relieve the pain. Sooner or later, other signs of involvement of the spinal cord appear, such as changes in reflexes, weakness or paralysis of the legs, Babinski's sign and incontinence. Metastatic tumors also may involve the cervical portion of the spinal cord and cause radicular pain.

Lesions of the brachial plexus (figure 5)—Tumors—Neoplasms involving the brachial plexus may be primary, such as neurofibromas, or secondary, such as invasive soft-tissue tumors. Here the characteristics of the root type of pain are lacking and the pain and muscular weakness are found to coincide with the innervation from one of the cords of the plexus or a particular nerve rather than one root, as they do in cases of lesions of the roots or spinal cord.

Traumatic or traction lesions—Lesions from stabbing or gunshot wounds involving the brachial plexus are obvious causes for pain about the shoulder. Traction lesions involving the brachial plexus are fairly common. They may follow operations in which the Trendelenburg position is used with poorly padded shoulder rests; they may be seen in soldiers or hikers in the form of so-called pack palsy, when a heavy knapsack has been carried for a long period, with pressure on the brachial plexus.

Mechanical injuries—The remainder of the lesions involving the brachial plexus can be grouped best under the term mechanical injuries. These include the scalenus, the cervical-rib and the costoclavicular syndromes, all of which have one thing in common, namely, varying degrees of compression of the brachial plexus and the accompanying subclavian artery and vein. One can suspect the presence of this type of lesion when the patient is in the older age groups, when the pain or discomfort in the shoulder is diffuse and related to posture, and when it is accompanied by varying degrees of numbness, coldness and tingling of the arms and fingers. The pain lacks the sharp knifelike quality of root pain; it is not increased by movements of the head; it may be relieved by different postures of the arm, and it may be aggravated by certain actions, such as lifting, sleeping and weeding.

The cervical-rib syndrome is the best known of these mechanical injuries. It is produced by an anomalous cervical rib that compresses the elements of the brachial plexus and vessels as they cross over it to enter the axilla. One should keep in mind that a number of people who have cervical ribs, either short or long, never experience symptoms from them. When symptoms do develop, they usually appear later in life; they apparently are produced by sagging of the shoulder girdle as posture becomes poor, with resultant traction on the plexus. Downward traction on the arm usually increases the pain, whereas elevation

of the arm relieves it. Since the subclavian vessels also are compressed to a greater or lesser degree, there are usually coldness, numbness and tingling, generally distributed over the entire forearm and hand rather than along the path of any particular nerve. If one finds such a pattern in a patient and roentgenograms do not reveal a cervical rib, the presence of the scalenus syndrome must be considered.

The brachial plexus and vessels pass over the first rib just posterior to the insertion of the scalenus anticus muscle into the tubercle of the first rib. Hypertrophy of this muscle, with elevation of the first rib, may bring about compression of the nerves and vessels as they pass over the rib. An abnormally high first rib or a sagging shoulder girdle will have the same effect. Injection of procaine hydrochloride into the lower portion of the scalenus muscle may be of diagnostic aid; if such injection brings about complete relief, surgical section of the muscle becomes a better gamble. In some persons, the space between the clavicle and the first rib is abnormally narrow and the nerves and vessels passing through are compressed, giving rise to the relatively uncommon costoclavicular syndrome. Section of the scalenus anticus muscle fails to relieve this, whereas resection of the first rib does bring relief.

Serum neuritis—This condition results from the use of serum, particularly horse serum. Serum sickness, with urticaria, arthralgia, lymphadenopathy and fever, occurs 3 to 10 days after the injection. The signs of neuritis usually appear a few days after the serum sickness. Pain develops in one or both shoulders, accompanied by minor paresthesia. This form of neuritis appears to have a predilection for the right upper extremity, particularly the muscles supplied by the fifth and sixth cervical segments. Residual weakness and atrophy of these muscles frequently follow.

Lesions of peripheral nerves—Lesions of peripheral nerves may cause pain in the shoulder secondarily through disuse brought on by loss of muscular power or by causalgic states in which the arm and hand are held immobile to alleviate the burning pain in the hand.

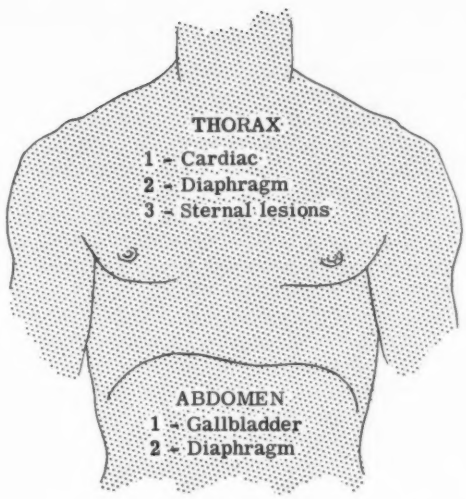

FIGURE 6. Thoracic and abdominal lesions that should be considered early in examination.

Thoracic lesions (figure 6)—Cardiac disease—The primary cause of pain in the shoulder originating in the thoracic cage may be cardiac disease. The pain referred to the shoulder in angina pectoris or acute coronary occlusion is well known and needs no further comment. Persisting pain in the shoulder is frequently used as a guide to progress, and the patient is admonished to continue to rest in bed while such pain is present. One should be wary in following such a plan, for the pain in the shoulder actually may be the first sign of sympathetic dystrophy and may not be caused by persistent myocardial insufficiency at all; in such cases, rest in bed is certainly contraindicated.

Pleurisy—Inflammatory lesions involving the diaphragmatic pleura frequently give rise to a painful shoulder. However, the respiratory pain, increased erythrocytic sedimentation rate, leukocytosis and malaise indicate the primary disorder in the pleura.

Tumors—Mention should be made of tumors of the superior pulmonary sulcus. These frequently produce a neuritic type of pain in the shoulder and arm, atrophy of the small muscles of the hand and Horner's syndrome. Thoracic roentgenograms reveal a shadow in the apex of the lung. This group of findings is

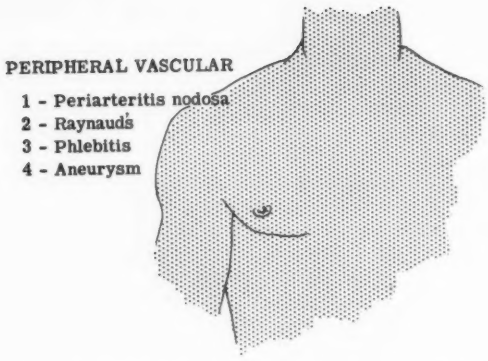

FIGURE 7. Peripheral vascular lesions that should be considered in differential diagnosis of pain in the shoulder and arm.

commonly referred to as Pancoast's syndrome; the cause is usually primary bronchogenic carcinoma involving the brachial plexus and sympathetic chain.

Esophageal spasm—This may produce pain referred to the neck, shoulders and arms. Esophageal hiatal hernias of the diaphragm frequently produce pain in the arm.

Peripheral vascular disease (figure 7)—This rarely produces pain in the shoulder. The symptoms are primarily in the forearm and hand. These may lead to voluntary restriction of motion of the shoulder to protect the hand, and thus might bring about disuse and pain in the shoulder.

Treatment

If the mechanism initiated by the primary disorder, as depicted in the afore-mentioned figure, is allowed to operate long enough, it becomes self-sustaining, even though the original source of the pain in the shoulder is removed. Thus, it is important that the physician correctly assess the situation early in the course before this vicious circle has become established. The most efficacious and simplest way is to diagnose correctly the primary disorder and initiate appropriate treatment.

If a tear in the rotator cuff is found, the treatment of choice is surgical repair. If for sound reasons operation is not indicated, conservative measures of rest, administration of cortisone, corticotropin (ACTH) or hydrocortisone (HYDROCORTONE®) and graduated exercise can be carried out. If a protruded cervical intervertebral disk is found to be the initial cause of the painful shoulder, conservative treatment consisting of heat, massage and traction on the neck is given a fair trial. If no improvement ensues or if the neurologic deficit progresses, surgical intervention is indicated (figure 8). If rather than a protruded disk there is found to be, as the result of arthritis, a ridge on a vertebra compressing the nerve root or if osteoarthritic narrowing of the intervertebral foramen is giving rise to the root pain, surgical decompression can be carried out, with removal of the lamina on the involved side (figure 9). Enough bone should be removed to allow adequate decompression of the nerve root as it passes through the intervertebral foramen. Intramedullary or extramedullary tumors of the spinal cord can be successfully removed in the majority of cases by use of modern neurosurgical technics.

It obviously is beyond the scope of this presentation to consider the specific treatment of each of the primary disorders already listed. Once the correct diagnosis is made, therapy can be carried out readily. It is important to re-emphasize that once the pain in the shoulder becomes established it leads to disuse and stiffness that in turn lead to more pain. Therefore, even though the initial cause of the pain be removed, one is still faced with the problem of treating the residual painful stiff shoulder, plus the added changes in the hand, if such have appeared.

When confronted with a patient exhibiting any stage of this syndrome from the earliest, with only pain and stiffness in the shoulder, to the latest, with severe atrophic changes in the hand, the physician must realize that he is dealing with a personality that is frequently refractory to treatment. Many of these patients do not religiously carry out the recommended exercises and medication. Because their tolerance to pain is low and the exercises temporarily increase the pain, they are loath to carry out the exercises unless constantly supervised and encouraged. The physician should accept this responsibility and set up a rigid

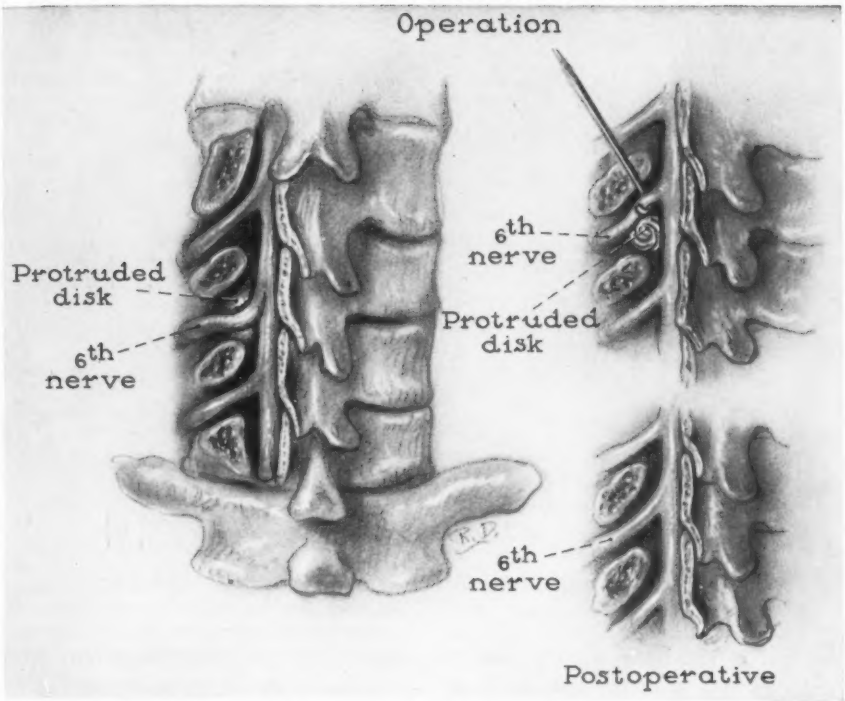

FIGURE 8. Removal of cervical intervertebral disk by means of hemilaminectomy, with decompression of nerve root.

routine of graduated physical therapy. The patient should be seen frequently; the progress or lack of it should be assessed, and encouragement given freely. Because of this dependency, use of narcotics always should be avoided but salicylates can be given to alleviate the pain, along with heat and massage. This regimen, when sympathetically supervised, will bring about satisfactory results in the majority of cases if it is started early in the course of the syndrome before the dystrophic changes have become severe. If this conservative course is given a fair trial and little or no improvement is seen, and particularly if the reflex sympathetic dystrophic changes are advancing, more vigorous management is indicated.

Good results have been obtained with (1) repeated procaine block of the stellate ganglion on the affected side, (2) parenteral administration of cortisone or ACTH or both, (3) injection of compound F (hydrocortisone) into the affected shoulder joint, and (4) surgical removal of the stellate ganglion and upper thoracic sympathetic chain. It would appear advisable to try the simpler measures first. If these do not bring about the desired relief, the other methods may be tried.

Steinbrocker, Neustadt and Lapin,[9] in 1953, reported on a series of patients who had the shoulder-hand syndrome and in whom the effects of cortisone and ACTH were compared to the effects of repeated procaine block of the stellate ganglion. Their results showed that on the whole sympathetic block gave somewhat better results than did use of ACTH or cortisone, although the results of either treatment in the earlier phases were extremely good. Once the repeated block gave a satisfactory response, maintenance therapy was not required, while management with ACTH and cortisone required a period of mainte-

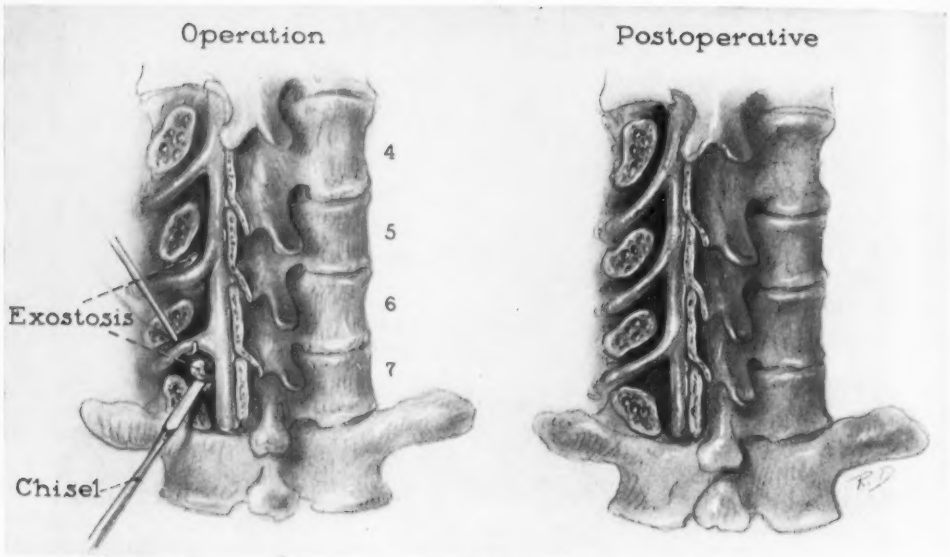

FIGURE 9. Relief of osteogenic compression of nerve root by means of hemilaminectomy.

nance therapy. It was their opinion that repeated stellate block probably was the treatment of choice, with administration of ACTH and cortisone a close second.

Disadvantages are inherent in each form of treatment, of course. It takes a trained person to carry out safely block of the stellate ganglion. The dangers associated with cortisone therapy are well known; it may precipitate a previously quiescent gastric ulcer or it may mask an active infection. Recently, some workers have been injecting compound F (hydrocortisone) directly into the affected shoulder joint. This temporarily alleviates the pain in the shoulder and allows active exercise, thus overcoming the disuse and stiffness. Such treatment encourages the patient by demonstrating that the pain can be effectively controlled. The injection may have to be repeated several times, and an active program of physical therapy is carried out simultaneously.

The beneficial effects of all these methods are limited to those patients who have early changes in the hand, such as vasodilatation, increased surface temperature, stiffness and painful swelling. When changes in the hand are more advanced, with a dry, pale or cyanotic hand that shows beginning atrophy, the results are not so good. However, block of the stellate ganglion is a helpful procedure. It may give relief in addition to its role as a therapeutic test. If the block gives partial or only temporary relief, surgical removal of the stellate ganglion and upper thoracic sympathetic chain is indicated. When repeated sympathetic block is unsuccessful, the results to be expected from surgical intervention are uncertain. As was pointed out previously, not all the sympathetic innervation of the upper extremity is carried through the stellate ganglion. Some of the fibers apparently pass out of the spinal cord via the ventral roots of the cervical segment of the spinal cord and are intimately associated with the peripheral nerves throughout their course to the hand. It is, of course, not feasible to attempt to interrupt these fibers, and this may explain the uncertain results following sympathectomy.

It must be emphasized that, whichever method is selected, all patients require salicylates to relieve the pain, graduated and supervised physical therapy, and encouragement.

If the presence of a protruded cervical disk or other intraspinal lesion is suspected, myel-

ography with ethyl iodophenylundecylate (Pantopaque) may be indicated, as well as examination of the cerebrospinal fluid. With roentgenologic confirmation of the presence of the lesion or with other evidence of the lesion in the results of examination of the cerebrospinal fluid, cervical laminectomy is necessary to remove the tumor or disk and decompress the cervical nerves.

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BOOKS RECEIVED

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews will be found in this issue starting on page A-102.

Drugs in Current Use 1955. Edited by Walter Modell, M.D., F.A.C.P., Associate Professor, Clinical Pharmacology, Cornell University Medical College, New York. 147 pages. 1954, Springer Publishing Co., Inc., New York. $2.00; 10 or more copies, $1.80 each.

Normal Labor. By Leroy A. Calkins, M.D., Ph.D., Professor and Head of the Department of Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City. 128 pages. 1955, Charles C Thomas, Springfield, Illinois. $4.00.

Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract. By John Russell Twiss, M.D., Assistant Professor of Clinical Medicine, and Elliot Oppenheim, M.D., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School, New York. 653 pages with 136 illustrations. 1955, Lea & Febiger, Philadelphia. $15.00.

Reactions with Drug Therapy. By Harry L. Alexander, M.D., Emeritus Professor of Clinical Medicine, Washington University Medical School, St. Louis. 301 pages with 33 illustrations. 1955, W. B. Saunders Company, Philadelphia and London. $7.50.

Correlative Neurosurgery. By Edgar A. Kahn, M.D., Robert C. Bassett, M.D., Richard C. Schneider, M.D. and Elizabeth Caroline Crosby, M.D., Department of Surgery, Section of Neurosurgery, University of Michigan Medical School, Ann Arbor, with 11 contributors. 413 pages with 235 illustrations. 1954, Charles C Thomas, Springfield, Illinois. $19.50.

Peripheral Vascular Diseases. By Edgar V. Allen, M.D., Nelson W. Barker, M.D., and Edgar A. Hines, Jr., M.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Ed. 2. 825 pages with 316 illustrations, including 7 in color. 1955, W. B. Saunders Company, Philadelphia and London. $13.00.

Diseases Transmitted from Animals to Man. By Thomas G. Hull, Ph.D., Secretary, Council on Scientific Assembly; Director, Bureau of Exhibits, American Medical Association. Ed. 4. 717 pages with 104 illustrations. 1955, Charles C Thomas, Springfield, Illinois. $12.50.

Medical Care for Tomorrow. By Michael M. Davis, Ph.D. 497 pages. 1955, Harper & Brothers, Publishers, New York. $6.50.

Prepayment and the Community. Edited by Harry Becker, Associate Staff Director of the Commission on Financing of Hospital Care. 356 pages with illustrations. 1955, The Blakiston Division, McGraw-Hill Book Co., Inc., New York. $4.50.

Diabetes Mellitus; Objectives and Methods of Treatment. By Henry T. Ricketts, M.D., Professor of Medicine, University of Chicago School of Medicine, Chicago. 123 pages. 1954, Charles C Thomas, Springfield, Illinois. $3.25.

The Coagulation of Blood: Methods of Study. Edited by Leandro M. Tocantins, M.D., Professor of Clinical and Experimental Medicine; Director, Charlotte Drake Cardeza Foundation, Jefferson Medical College, Philadelphia, with 18 contributors. 240 pages. 1955, Grune & Stratton, Inc., New York and London. $5.75.

Clinical Diagnosis. By Elmer G. Wakefield, M.D., F.A.C.P., Mayo Clinic and Mayo Foundation, Rochester, Minnesota. 1,605 pages with 135 illustrations. 1955, Appleton-Century-Crofts, Inc., New York. $22.50.

DIAGNOSTIC CLINIC

Common Sense in Cancer

GEORGE CRILE, JR.*

The Cleveland Clinic Foundation, Cleveland

A STEADILY increasing number of patients believe that surgical procedures spread cancer and shorten life. Some even ask that nothing be done if cancer is found. This belief is rising in spite of strong propaganda in support of an early and radical surgical attack. Who are right—the people or the ultraradical cancer surgeons? There is much to be said on both sides.

GEORGE CRILE, JR.

In many respects cancer cells are like bacteria. Dr. Cornelius Rhoads of the Sloan-Kettering Research Institute has made an analogy between the metabolism of cancer cells and the metabolism of bacteria. This analogy can be carried further, for there is also a similarity between the behavior of cancer cells and the behavior of bacteria.

Some cancer cells are like the most virulent hemolytic streptococci—before they cause any local symptoms they may have spread into the lymphatic system and blood stream. Figure 1 is a picture of cancer cells recovered from the mesenteric blood of a patient with what is clinically called an "early" cancer of the colon. Figure 2 shows cancer cells from the blood of a patient with a more advanced cancer. The blood is filled with cancer.[1]

Cells are continually exfoliated by cancers. The best example of this is the multitude of cancer cells found in the vaginal secretions of patients with cancer of the cervix. As the cells invade blood and lymphatic vessels, there is nothing to prevent their migration into the moving streams of body fluids. This is the way infection is spread. This is the way metastases are born.

Incision and drainage do not help the lymphangitis or the cellulitis of a virulent streptococcal infection. Operation breaks the barriers of natural resistance and spreads the

*The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

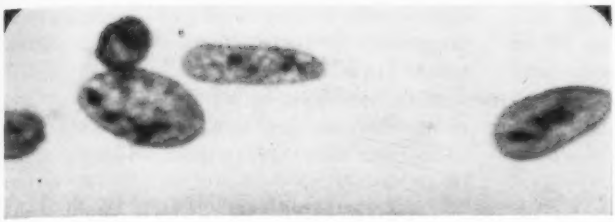

FIGURE 1. Cancer cells from mesenteric blood in "early" cancer of the colon.

disease. We need only recall the days before sulfanilamide when a girl would prick a pimple with a pin and the next day she would be dead.

Surgical attacks on highly malignant tumors, like trauma to streptococcal infections, may do more harm than good. They break the natural barriers. They spread the disease. When we remember that the blood and lymphatic vessels of highly malignant tumors are filled with tumor cells, it is clear that it is not often possible to excise such tumors completely. They have extended diffusely into the tissue spaces. They are systemic diseases. In cases of such tumors, the people who think that surgery does harm are right. Even when these cancers are detected early, even when they are treated by operations of the most radical scope, the disease is rarely checked by surgery. Tissue spaces are opened. Cancer cells gain further access to blood vessels and lymphatics. Cancer cells are seeded in the incision and in the peritoneal cavity. When the tumor is spreading diffusely, it is best to leave it alone.

Not all cancers are as virulent as hemolytic streptococci. Some are like staphylococci—locally destructive, tending to remain in one area. These cancers are like abscesses. They are amenable to surgical treatment. Squamous cell cancers, papillary cancers of the thyroid, and many of the cancers of the colon are biologically predetermined to remain localized for long periods and to metastasize chiefly to the regional lymph nodes. Many of them can be controlled by adequate excision of the primary tumor and its zone of lymphatic metastasis. The people who consider surgical attack harmful are wrong about these tumors. Most of them are curable.

The public does not distinguish between various types of cancer. They lump cancers together under one name. That is why the cancer problem is not understood. But if we are to settle the confusion in the mind of the public, we must first settle the confusion in our own minds. We must study the natural history of cancers.

Cancer is not a special problem to be treated always in the same way. Each cancer is a separate problem. Because a radical operation is well adapted to the biology of a squamous cell

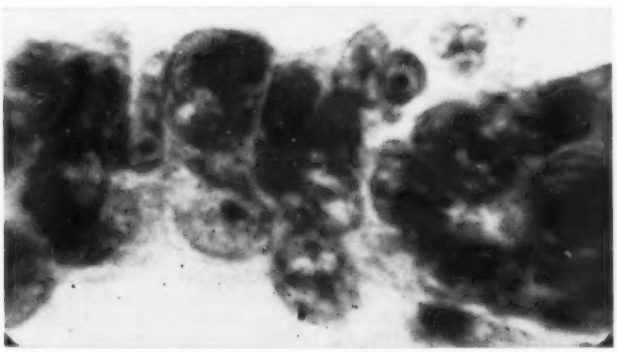

FIGURE 2. Cancer cells from the blood of a patient with more advanced cancer.

cancer of the jaw, it does not mean that radical surgery will give the best results in an undifferentiated cancer of the breast or pancreas. Nor does it mean that a basal cell cancer of the skin, an early cancer of the lip, or a papillary cancer of the thyroid must be treated by the same type of mutilating operation that is necessary to control the cancer of the jaw.

Operations even for low-grade cancers, if not well planned, may do more harm than good. Even a low-grade cancer can be implanted and made incurable by biopsy in the surgical field or by an operation which cuts into the tumor. Papillary cancers of the thyroid, if left alone, may grow slowly for 30 years or more without damage to the patient. They may sclerose and not grow at all. Similar tumors, if cut into, may become devastatingly invasive.

"Palliative" operations that cut through cancer are not often palliative. They are disseminative. Abdominal tumors that were localized before operation may be seeded by the surgeon in the incision and on peritoneal surfaces. These implants arise from cells exfoliated in the lumen of a hollow organ or from cancer cut into and spread by the knife. The scalpel that cuts across cancer is like the wind; it scatters seeds.

There are two ways in which patients with cancer are harmed—two surgical practices that justify the belief that operation does more damage than good. One is inadequate operation on localized cancer. If this type of operation cuts through cancer, a potentially curable tumor may be made incurable. If a surgeon not trained to do a radical resection should unexpectedly encounter a localized cancer, he should do nothing. Even a biopsy may change a curable tumor into a hopelessly disseminated disease.

The second type of operation that does damage is the super-radical attempt to accomplish the impossible. Many of these operations are done by the masters of surgery. They are

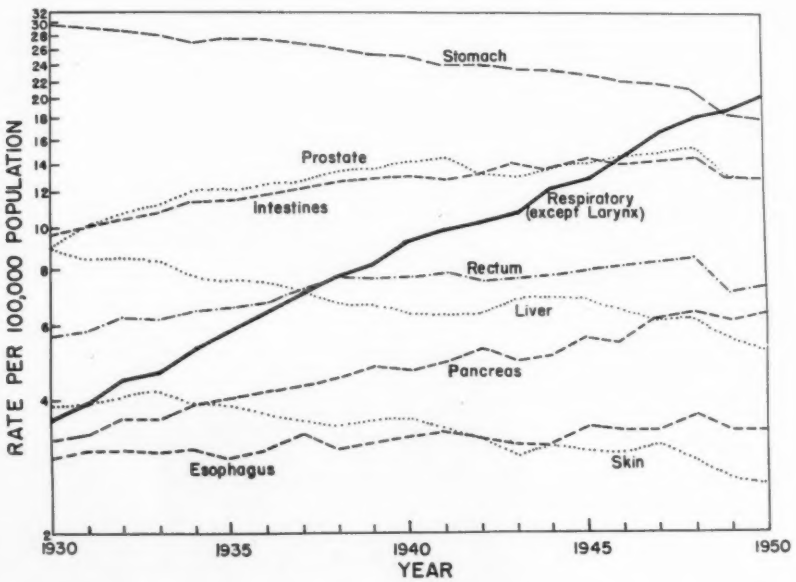

FIGURE 3. Death rates for various forms of cancer, United States, 1930 to 1950. (Standardized for age on the basis of the 1940 population. Source: National Office of Vital Statistics. Prepared by the Statistical Research Section, American Cancer Society, February 1954.) a. Death rates for cancer, white males.

done in specialized hospitals where there has grown up a philosophy that the presence of cancer justifies anything that the surgeon elects to do. Surgeons deeply imbued with this doctrine often refuse to recognize the hopelessness of certain cancers, even if these cancers have been documented as incurable. They do not admit that attempts to cure incurable cancers usually do harm. Patients submitting to radical operations for hopeless cancer suffer not so much from their cancers as from misguided attempts to control them. Their lives are shortened. They die in pain.

Fear of cancer should not be exploited. Surgeons should not subject their patients to useless operations in cancer's name. If these operations are done without cost to the patient as part of a planned research program, they may be justified until their value is proved or disproved. If they are done for high fees, then not only the wisdom but also the ethics of their authors are open to question. The expense of terminal care, even without surgical bills, is sufficient to bankrupt many families. If the cost of useless surgery is added, then even the standard of living and the education of the next generation may be sacrificed to meet the bills.

Great progress has been made in the treatment of certain types of cancer. Squamous cell cancer of the head and neck, cancers of the colon, and central recurrences of cancer of the cervix are better handled today than ever before. That is because this type of cancer is biologically adapted to radical surgical therapy. But in the vast majority of the common killing cancers—cancers of the stomach, lung, pancreas and breast—treatment has effected little change in death rates (figure 3).

If we have not been able to alter the death rate by increasing the scope of operations for cancer, can we do so by earlier diagnosis? The answer is "sometimes." In organs such as the cervix, where we can recognize and treat a cancer in its preinvasive stage, we can usually cure it. The same applies to cancer in

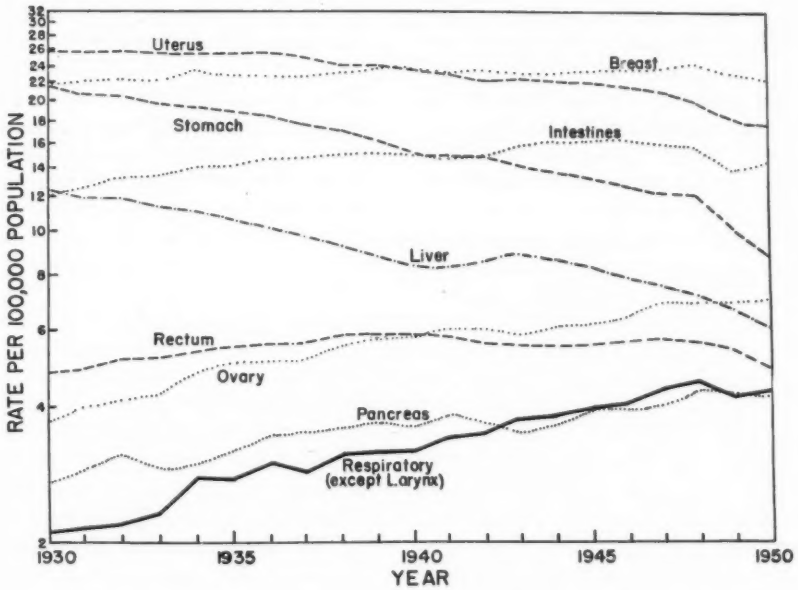

FIGURE 3. Death rates for various forms of cancer, United States, 1930 to 1950. (Standardized for age on the basis of the 1940 population. Source: National Office of Vital Statistics. Prepared by the Statistical Research Section, American Cancer Society, February 1954.) b. Death rates for cancer, white females.

rectal polyps, to early cancer of skin and lip, and to some cancers of mouth and colon. But in highly malignant tumors like many cancers of the breast, lung, pancreas and stomach, there is no conclusive evidence that early diagnosis and treatment alter the course of the disease. By the time these tumors are detectable by our present clinical methods, their biologic characteristics have sealed the patient's fate.

Statistics of five year cures are of little value in determining the effects of early treatment. A lump in the breast that has been present for five years may be proved at operation to be a cancer. This cancer, which for five years had no treatment, is already a "five year cure." The variations in the natural history of cancer are so astonishing that statisticians have stated that we cannot prove that any kind of treatment, regardless of how early it is given, alters the course of invasive cancer of the breast by over 10 per cent at most.[2]

No one would deny that the public should be shown the advantages of early treatment. If the course of cancer can be altered in even 5 per cent of those afflicted, public education is worthwhile. But is fear the best approach to education? Is it not possible that fear of cancer is now causing more suffering than early diagnosis can prevent? Perhaps the time has come to use an approach that is realistic and based on these truths: Low-grade cancers, if treated early, usually can be cured; high-grade cancers, regardless of treatment, usually are incurable. Cancer of the breast is one of the common cancers that raises this question.

All evidence points to biologic predetermination and resistance of the host as the most important factors in the survival of patients with cancer of the breast. Some surgeons are even suggesting that simple mastectomy and x-ray therapy are as effective as radical mastectomy in both the cure and palliation of breast cancer.[3] Yet there is a trend toward super-radical operations on the breast, with removal not only of breast and axillary nodes but also of clavicle, cervical nodes, and parts of the chest wall, and dissection of the mediastinum. The surgeons who advocate these operations are fighting the law of diminishing returns, a law which states that as operations for cancer are extended there is less and less increase in curability.

The super-radical operation for cancer of the breast, particularly as applied to lesions of the inner quadrant where the internal mammary nodes are the first line of defense, is an interesting and probably a worthwhile experiment. But the wisdom of reporting such an operation before time has established its value is open to question. The leaders of our profession wield an enormous influence, and their practices are widely followed. There is danger that their super-radical operations will be considered to be procedures of established value. The practicing surgeons of the country may be tempted to follow in the footsteps of their teachers. If they do, morbidity will ensue.

The technics of radical cancer surgery have been carried far into the zone of diminishing returns. The lowered mortality and the better understanding of the physiology of the surgical patient have made possible operations which a few years ago were not considered feasible. Although these operations often control low-grade cancers, they rarely cure cancers of high malignancy. This failure, and the fact that many of the patients are worse after operation than they would have been if left alone, are shaking the confidence of patient and physician in the surgery of cancer. If surgeons are to regain the confidence of the public and the profession, they will have to stop attempting the impossible. They will have to relearn the wisdom of conservatism. They will have to cultivate common sense in cancer.

This presentation is not the solution of a problem, it is the definition of one. There are many borderline cases in which none of us know whether it is better to be bold or to admit defeat. Our problem is to learn, and this we cannot do if we blind our eyes to our failures, if we refuse to recognize the damage we sometimes do. One fact is certain; the trend toward radical surgery has been carried too far. We must recognize the blunt fact that there are still two kinds of cancer, the operable and the inoperable. The problem is to learn which is which.

It is time to take a second look at the problem of cancer. We have seen the maximum

mutilation that patients can be subjected to and still survive. Now we must develop operations that give as much control of cancer as is possible, but with the least possible deformity, with the least impairment of function.

Fortunately, there is hope for the future. The slowly growing cancers, whose cellular metabolism is almost like that of normal cells, are the cancers in which surgery is effective. The rapidly growing cancers whose metabolism is different from that of normal cells are the ones in which chemical treatment in experimental animals has proved most effective. The patient work of the chemist, supported by a wise, generous and far-sighted public, promises to control the cancers surgery cannot cure.

But the day of the chemical cure of cancer is not yet here. We are still living in the era of surgery, and until the problem of cancer is solved we must do the best we can with the tools at hand. These tools are good and useful if they are employed with wisdom and skill. The same tools are dangerous and harmful when they are used recklessly.

When we cannot cure, we must be careful that at least we do no harm. We must be considerate of the financial plight of families faced with the problems of terminal care. If we follow these principles and if we continue to improve the treatment of those cancers that are curable, there will be no cause for the people to lose faith in our profession.

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Postgraduate Clinical NOTES

33. EXPERIMENTAL MEDICINE

All operations are of their nature experimental; the statistical results are broadly known and from them the general impersonal risks can be calculated. In some, what concerns us most is danger to life itself; in others fatality can be almost excluded and the experimental side depends on the success that can be expected, the relief that can be anticipated in the individual instances. No statistics have so personal a message. If it comes to that, all medical treatment is also experimental. As Professor Pickering has pointed out, the prescription even of rest in bed for two or three weeks, or of a bottle of cough mixture, are experiments, the results of which deserve closer observation and quantitative analysis than they get.

Sir Geoffrey Jefferson, *Lancet*, January 8, 1955, p. 59

Arterial Stenosis: A Correlation of Clinical and Angiographic Findings

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GEZA DE TAKATS

ARTERIAL stenosis is not the equivalent of arteriosclerosis. An artery may become narrow for many reasons. Unfortunately, most physicians, particularly surgeons, see cases of arteriosclerosis and arterial stenosis only in the terminal phase.

I will describe the early findings in arterial stenosis, a disease which usually terminates with gangrene, as illustrated in figure 1. The only problem in such a case of arteriosclerotic gangrene is when to amputate and at what level. A careful study of the histories of patients such as this one will disclose that except for about 5 per cent whose gangrene resulted from embolism and another 5 per cent in whom it was due to Buerger's disease, the majority had a slow, gradual onset of their disability over a period of some years, beginning with intermittent claudication.

Intermittent claudication is, in itself, an important localizing symptom. If a patient has claudication in the calves, the obstruction is located around the popliteal artery; when the claudication is in the thighs, the obstruction or stenosis is much higher, in the upper end of the femoral or the lower end of the iliac artery; pain in the buttocks or lower part of the thigh indicates almost certainly that the obstruction is in the lower part of the aorta or in the iliac artery.

If, in addition to intermittent claudication, a patient has a diminished pulse in one femoral artery compared with that in the other, or in one popliteal artery compared with the other, this finding establishes very simply that a narrowing or a stenosis is present. There

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Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

FIGURE 1. Arteriosclerotic gangrene.

are, however, more sensitive methods of examination available.

In arterial stenosis, an atheroma produces a stricture, a stenosis, of the artery. This atheroma is well vascularized; it is full of blood vessels which help to establish a collateral circulation, and these blood vessels rupture very easily. In fact, one of the most frequent causes of complete occlusion in arterial stenosis is a hemorrhage into the wall of the artery. This has medicolegal significance, because again and again we see patients who either do not have symptoms or have minimal symptoms of vascular disease in whom occlusion of a vessel follows comparatively minor trauma. It must be admitted that this constitutes aggravation of a pre-existing disease. The best way to demonstrate such pre-existing disease is to establish that it is present in the opposite extremity, because in most such cases the involvement is bilateral.

The oscillometer is merely an ordinary blood pressure apparatus with a sensitive needle which registers the pulse volume. The chart in figure 2 shows the oscillometric curves in a case of stenosis of the left iliac artery. The pulsation in the patient's foot is good. At 100 mm. of mercury the needle swings about 1.5 cm. When the patient stands up, the curve becomes higher and shifts over to the right. That means simply that there is hypertension in the extremity, which all of us have in the erect position.

One reason that arterial stenosis affects predominantly the lower extremities is the continuous vasoconstriction necessary to maintain the blood pressure, and the increased tension in the vessels. Note in figure 2 that the oscillometric curve becomes much smaller when the patient exercises. In other words, here is actual graphic evidence that the circulation is adequate in the resting state but inadequate for any exercise. An exercising muscle requires 20 to 30 times as much blood as a resting muscle. We must examine patients with vascular disease not only in the horizontal position—in a basal state, resting—but also after exercise. The symptom that brings the patient to the physician, namely, cramping on walking, is the most important, the

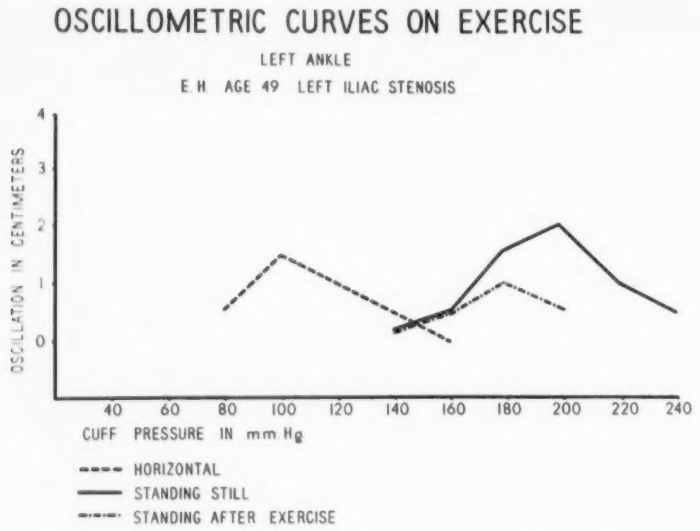

FIGURE 2. Results of oscillometric study in a case of stenosis of the left iliac artery.

dominant symptom of arterial insufficiency.

Examples of arterial stenosis in its early stages are illustrated in figures 3 to 10. Most patients I have seen with severe vascular insufficiency in one leg have had early evidence of the same condition in the opposite leg. The patient whose arteriogram is shown in figure 3 lost his other leg below the knee because of progressive arterial stenosis of the popliteal artery, which finally became completely occluded. This final occlusion may be due to trauma, to a sudden fall in blood pressure, to a sudden increase in the clotting activity of the blood, to hemoconcentration, or to one of many factors. If one examines the opposite leg, one will note a slight arterial narrowing. The extensive involvement in the other leg masked the findings in the one shown in figure 3. The patient has few symptoms; he still has an open pulse, but he will tire easily. Later on I will discuss what can be done to prevent the spontaneous progression of this disease.

In figure 4 can be seen slight narrowing of a vessel, just a slight loss of smooth contour. Curiously, the patient had considerable symptoms. He could walk three or four blocks slowly but not fast; he could not climb more than one flight of stairs without pain. He could walk on grass but not on pavement. He could walk leisurely and window shop with his wife, which as you know is a most expensive procedure, but he could not trot to catch the 8:06 in the morning. As you know, some persons are more sensitive to pain than others. This man had claudication even though we could not find any other vascular involvement except this slight narrowing.

A case of more advanced obstruction is illustrated in figure 5. I have not included examples of massive occlusion, which is another story. The slight channel which can be seen in figure 5 was easily repaired. I simply resected the segment and anastomosed it directly. This patient, who is a cotton planter, did not require grafts, as some with more extensive stenoses do.

Figure 6 depicts a case which actually does not belong to this group because this is no longer a stenosis; it is an actual gap in the artery. It is, however, a very short gap with a very short, sturdy collateral circulation. The patient is entirely asymptomatic, and the pulses are good. In my opinion resection should not be done in this case. Nature has

FIGURE 3. Arterial stenosis; patient lost other leg because of progressive arterial stenosis of the popliteal artery.

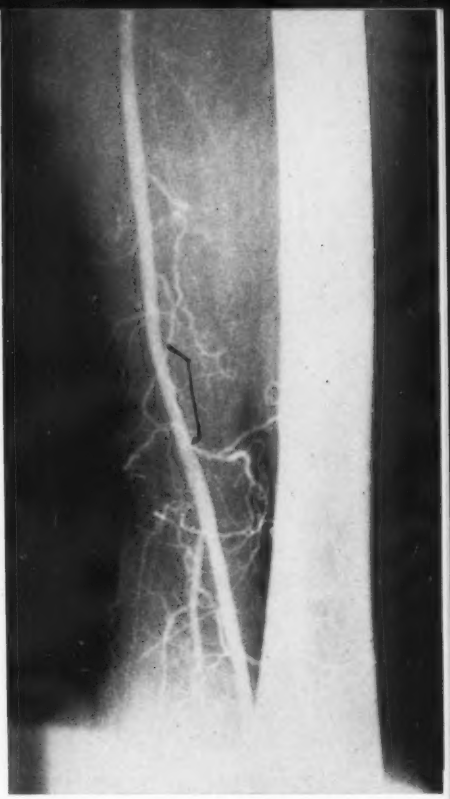

FIGURE 4. Slight narrowing (outlined in ink) and loss of smooth contour of vessel. Patient had claudication; no other evidence of vascular involvement could be found.

FIGURE 5. More advanced obstruction. The segment was resected and anastomosis performed. Grafting was not required.

FIGURE 6. An actual gap in an artery, but with good collateral circulation.

FIGURE 7. Stenosis of the right iliac artery. Patient had back pain.

FIGURE 8. More advanced stenosis. Treatment consists of opening the closed segment, reaming it out and resuturing it.

done a better piece of work here than any surgeon could.

The stenosis shown in figure 7 is in the right iliac artery. Again there were few symptoms, except that the femoral artery pulsated less vigorously on the right side than on the left and the patient had back pain, claudication in the thighs and buttocks. An orthopedic surgeon diagnosed this as disk, and I might say that if both disk and arterial insufficiency are present it is very important to keep the two causes of back pain separate, because relieving one cause will not relieve the other.

A more advanced case of stenosis can be seen in figure 8. Note the tortuous aorta and the diminished opacity of the opaque substance just below the bifurcation. A major catastrophe may result when occlusion occurs in this type of stenosis. In our clinic such patients are treated by opening up the closed segment, reaming it out and resuturing it, thereby obtaining patency of the vessel.

Very early stenosis is illustrated in figure 9. The patient is a 38 year old man, the principal of a high school. His occupation requires that he go up and down stairs a great deal. After one flight of stairs he had classic claudication, not in the foot or the calf, but in the posterior aspect of the thigh and in the buttocks. In this case, too, the vessel was reamed out, so to speak, and the patient now has full use of his limb and no symptoms.

An aortogram of a patient who already has had bilateral lumbar sympathectomy but has an almost complete occlusion at the bifurcation of the aorta is shown in figure 10. Again, the stenosis is characterized by back pain. The patient also has loss of erection because the middle sacral artery is gone.

At present, in our clinic and in many others, massive arterial occlusion is treated by resection and graft. That is not, however, the point I wish to emphasize. I want to bring to your attention the fact that at least 85 to 90 per cent of these patients have early symptoms which can be recognized by simple clinical means—by attention to decrease and difference in pulses and, if you have an oscillometer available, by the difference in the swinging of the oscillometric needle.

The next step, of course, is aortography and arteriography. Recently, reports have appeared in the literature warning that these procedures are dangerous. I consider them to be simple, harmless procedures, provided the patients are selected carefully and provided also that one or two men in any institution are assigned to carrying them out. It is certainly true that the average rotating resident who stays on a service three or six months cannot do them. We have utilized arteriography in more than 600 cases and have had no difficulty. At present, arteriograms are made of every patient who comes to the hospital because of segmental vascular disease.

I would like to talk with a patient who was sent to us by the University of Minnesota and who has kindly consented to be here today. She is 65 years old. (To the patient): Is that correct?

PATIENT: Sixty-six.

DR. DE TAKATS: You had difficulty in walking, with pain in the left calf, for about a year. Is that right?

PATIENT: Yes.

DR. DE TAKATS: Only one year?

PATIENT: Yes.

DR. DE TAKATS: What did you notice first? What was the difficulty?

PATIENT: Pain would come on after I had walked half a block.

DR. DE TAKATS: According to her history, the pain was so severe that finally she could walk only half a block, and there were no pulses felt below the femoral arteries. I note, in checking the pulses now, that both femoral pulses are bounding, and that is significant because they were absent.

She was admitted to the University of Minnesota Hospital and x-rays were taken. They revealed definite narrowing of the left common iliac artery, but good filling of both femoral arteries. That is very important. It means that the occlusion is segmental or the stenosis is segmental, that it is possible for a surgeon either to resect the segment if it is completely occluded or to ream it out if it is only stenotic.

On November 10, 1953, thrombo-endarterectomy of the left common iliac, hypogas-

FIGURE 9. Early stenosis.

FIGURE 10. Almost complete occlusion at the aortic bifurcation. Patient already had undergone bilateral lumbar sympathectomy.

tric and internal iliac arteries was done.

This patient's history indicates that the clinical examination is of primary importance, followed by laboratory study and roentgenography. She has obtained complete relief. Is that right?

PATIENT: That is right.

DR. DE TAKATS: How far can you walk now?

PATIENT: Indefinitely; nothing bothers me.

DR. DE TAKATS: Do you have to climb stairs?

PATIENT: Yes.

DR. DE TAKATS: How many flights?

PATIENT: Just one flight, but it is a long flight and it doesn't bother me at all.

DR. DE TAKATS: Were you relieved right after you left the hospital?

PATIENT: I was a little weak, for a while, but I was walking.

DR. DE TAKATS: Could you walk a mile now?

PATIENT: I could walk more than that if I had to.

DR. DE TAKATS: She has not been prompted, because I didn't do the surgery.

Interestingly, although there has been tremendous clinical improvement in this case, an aortogram taken after operation does not show any change from the previous one. The only way I can explain that, since the femoral pulses are so bounding, is that aortography is not infallible. As you know, the technic is much concerned with timing. It may be that the film was taken just a second or two too late and the opaque substance had disappeared from that segment. Anyone who could walk only half a block before thrombo-endarterectomy and can walk eight city blocks afterward has improved tremendously. (To patient:) Thank you for coming.

A few words should be said about the follow-up of these patients because here, as in many other fields of surgery, what we really want to know is how long will the improvement last? We have been doing thrombo-endarterectomies for four years, and are fairly confident that if the operation is to fail it will do so at the time it is performed.

In a series of 31 patients—which is a very small group, but, of course, we select them rather carefully—five patients left the operating room in the same pulseless state in which they came. What happens is that the blood clots immediately after the vessel is reamed out. This has to do with technical procedure or it may be related to something which is beyond us, namely, some atheroma below which produces a damming up of blood and prevents patency of the vessel. If the patient leaves the hospital with open, patent vessels, it has been our experience that the results are lasting. Our experience is most encouraging, because it means that certain types of arterial stenosis are segmental, occluding one vessel and not another, or that if occlusion takes place only the distal vessel will be invaded. The terminal gangrene illustrated in figure 1, the end result of arterial stenosis, may well be prevented by paying attention to these early symptoms.

One other operation I would like to mention is sympathectomy. In many of these cases the stenosis or the occlusion is diffuse; it may extend throughout the entire femoral, both superficial and deep femoral arteries; it may be at the popliteal level or below it; it may occlude the entire aorta clear up to the renal vessel. Obviously it would not be possible technically to resect or ream out such an occlusion.

Sympathectomy will not, of course, open a closed vessel. It will tend to decrease resistance in the collateral channels so that they will function better, and it opens up the arteriovenous communications in the periphery so that capillary circulation or terminal arterial circulation will be improved. A patient who has a sympathectomy probably will not be able to walk very much farther after operation than before, but he is better protected from gangrene.

Whenever you see a patient with diffuse obliterative vascular disease in one extremity, I urge you to pay a great deal of attention to the opposite extremity, because it ultimately will be involved to the same degree unless preventive measures are instituted.

At present (and I say this with some trepidation), we know of no dietary or pharmaceutical measure which would prevent the progressive stenosis and obliteration of the peripheral arterial tree.

Repair of Atrial Septal Defects During Hypothermia

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OPEN intracardiac surgery is becoming practical. With the blood flow through the heart interrupted, a surgeon may open the organ and repair certain defects under direct vision in a dry field. This new type of surgery has been accomplished with the use of heart-lung machines,[1] cross circulation,[2] and hypothermia. The latter method is the simplest, it provides the clearest operating field, and it has been of particular interest to us. We have used it experimentally to operate within all the cardiac chambers, and we have used it clinically to repair atrial septal defects,[3] with some success.

Defects of the atrial septum allow a shunt of blood from the left side to the right side of the heart and produce a clinical picture similar to that of ventricular septal defects or patent ductus arteriosus. They have been repaired by blind technics.[4,5] However, since many of them have complicated structures, an operation in which the surgeon can actually see what he is doing provides the best hope of obtaining an accurate repair.

Such an operation may be done during hypothermia by using a simple technic. When the body temperature is lowered, the metabolic rate is reduced. Consequently, oxygen requirements are so low that total vascular occlusion at the heart may be sustained for a much longer period than is possible at normal temperature.[6] Thus the inflow channels of the heart may be occluded and a dry intracardiac field obtained long enough—up to 10 minutes—to close atrial septal defects carefully with stitches.

Technic

The patient is anesthetized with PENTOTHAL® sodium and curare. Electrocardio-

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FIGURE 1. An anesthetized patient has been wrapped in the refrigerating blankets which are cooled by a cold alcohol solution being pumped through them.

graphic leads are attached, and a recording rectal thermometer is adjusted. Cooling is then started. The patient is wrapped in refrigerating blankets made of two layers of rubberized cloth. Between the layers is sewn a long rubber tube. The blankets are cooled by pumping an alcohol solution at 25° F. through this tube (figure 1).

Anesthetic agents are administered in sufficient amounts to prevent shivering. In from one to three and one-half hours the patient's temperature falls to 86° F. At this point cooling is discontinued and the operation is started. The temperature continues to fall, however, without further surface cooling, until it reaches a level of 79° F. to 82° F. at about the time the intracardiac procedure is to be performed.

The operation is performed with the patient in the supine position. The chest is opened through an anterior, transverse, submammary incision, and both pleural cavities are entered through the fourth interspaces. The sternum is divided transversely at this level to provide excellent exposure of the heart (figure 2a).

In preparation for the inflow occlusion, loops of polyethylene tubing are passed around the superior and inferior venae cavae and both lung roots are encircled with loops of twill tape. Before the open repair, the interior of the heart is explored with a finger inserted through the right auricular appendage. This exploration is an important step, for it enables the surgeon to learn enough about the defect to plan the precise details of the open repair.

Before the heart is opened, all the inflow and outflow channels are occluded. First the venae cavae and then the pulmonary roots are interrupted in order to close the pulmonary veins, and finally the aorta and pulmonary artery are clamped (figure 2b). A longitudinal incision is made in the right atrium and the defect is exposed and repaired with a running stitch of 2-0 or 3-0 silk plus additional interrupted stitches (figure 2c, d). In many cases the exact placement of the stitches has been crucial.

As the last stitch is tied down, the left auricle is filled with saline solution injected through a small tube lying in the defect (figure 2e). This is necessary in order to wash air out of the left side of the heart. The right auricle is then filled with saline solution, and the wound edges are elevated and closed with a clamp. Circulation is resumed by releasing all the occluding loops and clamps before the auricular wound is repaired.

The total period of interruption of circulation has varied from three and three-fourths to seven and three-fourths minutes.

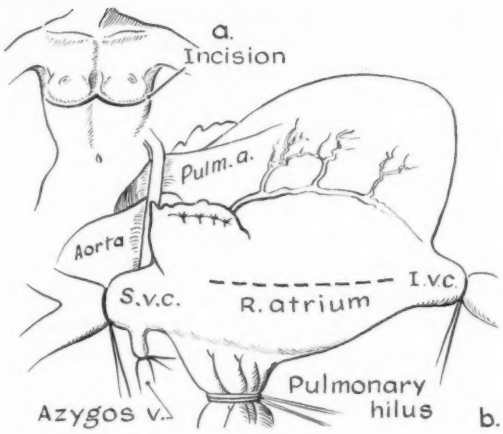


FIGURE 2a. Transverse submammary chest incision. The sternum is divided transversely and the chest is entered through both fourth interspaces.

FIGURE 2b. The circulatory inflow has been occluded by interrupting both venae cavae and by occluding both pulmonary roots. The outflow has been interrupted, as well, by occluding the pulmonary artery and aorta.

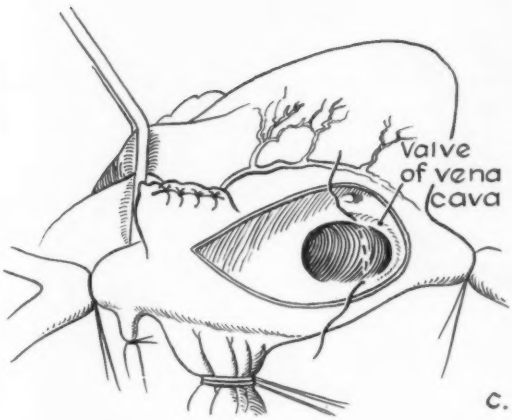


FIGURE 2c. The atrium has been opened widely, exposing the defect. The first stitch in the repair has been placed to avoid occlusion of the inferior vena cava.

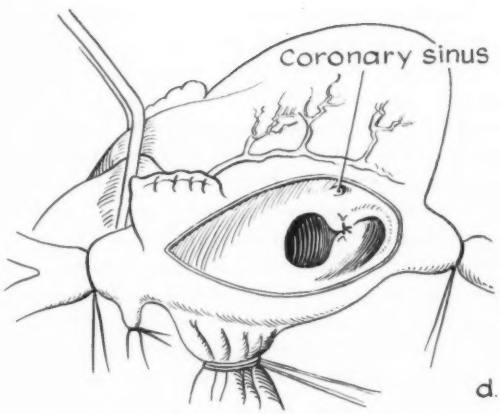
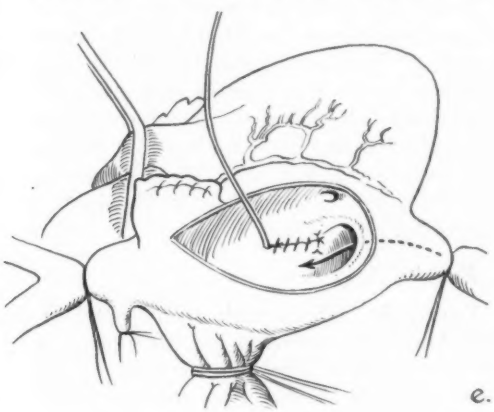


FIGURE 2d. First stitch of the repair has been tied.

FIGURE 2e. Repair has been completed but the tube used to fill the left heart with saline is still in place.



(Illustrations reproduced courtesy of *Surgery*.)

FIGURE 3. Patient being warmed in hot water bath which is kept at a temperature of 45° C.

During the operation the refrigerating blankets remain beneath the patient, but the liquid they carry has been heated to 114° F. This produces a slow elevation of body temperature which is accelerated, after the chest is closed, by immersing the patient in a bath of hot water (114° F.) until his temperature rises above 90° F. (usually 30 to 45 minutes) (figure 3).

Results

Twenty-six patients with atrial septal defects have been operated on. Their average age was 22 years. The oldest patient was 52 years old, and 13 were over the age of 21. Seventeen were females and nine were males. In one case the operation was abandoned before cardiotomy was done.

There were three operative deaths. One was due to a technical error resulting from our incomplete understanding of what proved to be a complicated defect. Digital exploration before the open operation, which was not done in this early case, has largely eliminated the possibility of repeating this type of error.

The second death occurred suddenly on the third postoperative day in the case of a 46 year old woman with a septum primum defect. She had a complete heart block after the operation, apparently as a consequence of the repair. Since a cause for her sudden death was not found at autopsy, we have attributed it to cardiac arrest as a result of the heart block. Another patient with a septum primum defect was operated on and he, too, now has a complete heart block. In repairing these low defects it is apparently difficult to avoid injuring the conduction system. At some point along the margin of this particular type of defect, the conduction bundle probably is placed in an exposed position close to the edge. Perhaps injury to this area can be avoided by altering the style of the repair.

The third death was due to irreversible ventricular fibrillation which occurred in the case of a 39 year old man as the chest was being opened. This complication is a recognized hazard of hypothermia and we have encountered it in eight cases in this series. In the other seven cases, however, it was reversible when treated with massage, ADRENALIN®, and serial electric shocks. Except in this one case, we have found ventricular fibrillation to be a manageable though unwanted complication. In the case in which death occurred, and in one other case in which defibrillation was difficult, it occurred spontaneously prior to any direct heart trauma. In the six cases in which defibrillation was not difficult, it was associated with the trauma of the cardiotomy or the digital exploration. The course in the patient with irreversible fibrillation was distinctive in another respect. He was cooled rapidly with ice water[7] in a manner that we have found harmless in dogs, whereas the other patients

were cooled more slowly. In any case, it is apparent that this complication does still limit the safety of hypothermia. Along with other workers, we are conducting intensive experimental studies of ventricular fibrillation.

The patients who underwent operation for repair of atrial septal defects more than a few weeks ago all show clinical improvement, sometimes striking in its magnitude. Lung vascular shadows have shrunk promptly after surgery, but heart size has not changed significantly. More detailed follow-up studies will be the subject of another report.

Discussion

Surgery for repair of atrial septal defects is new, and as yet there is not sufficient evidence to establish one technic as superior to all others. Nevertheless, at least one fact supports our advocacy of an operation under direct vision: the frequency with which these defects are found to be complex. The defect was a simple hole in only 10 of the 26 cases. Six defects were of the type described previously,[3] in which the valve of the inferior vena cava forms a false lower edge of the defect. In addition, in three of these six cases at least one of the pulmonary veins emptied on the wrong side of the defect. In four other cases one or two of the pulmonary veins entered the heart on the wrong side of the defect. Two patients, already described, had septum primum defects, and three had mitral stenosis in addition to an atrial septal defect. Certainly for all these complex defects, except possibly the last three, there would seem to be an important advantage in making the repair under direct vision.

Digital exploration before opening the heart has been an essential step in repairing these complicated defects, providing a good, though not perfect, understanding of the defect and allowing efficient use of the limited time the heart is open.

When mitral stenosis was found in the three cases mentioned, a digital splitting of the commissure was done while the exploring finger extended through the defect into the left side of the heart.

In an earlier report[3] the danger of preoperative misdiagnosis, especially in young children, was discussed. Since then all the patients operated on with the preoperative diagnosis of atrial septal defect have actually had this defect and none have had the more difficult atrioventricular canal which we encountered earlier. This testifies to the increasing skill of the diagnosticians.

Summary

1. Hypothermia provides an effective method for repairing atrial septal defects under direct vision. The technic described has been used in 26 cases with three deaths.

2. The method may be used successfully on adults and has proved to be especially suitable for the complex defects which were found in half the cases.

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Herpangina and Herpetic Gingivostomatitis; Clinical Differentiation

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PHYSICIANS who examine ill children are very frequently confronted with a problem of differential diagnosis in cases in which fever is associated with lesions of the oropharyngeal mucous membrane. Two distinct entities are responsible for most such syndromes. One of these is herpangina, an acute infectious disease, caused by any of six strains of group A Coxsackie viruses. The other is infectious gingivostomatitis, caused by the virus of herpes simplex. The purpose of this report is to outline briefly the diagnosis of these two illnesses as confirmed by laboratory data.

In a typical case of herpangina (vesicular pharyngitis), the disease occurs in the summer, and is characterized by sudden onset of fever, often at night, with accompanying symptoms such as anorexia, dysphagia and sore throat. Vomiting, abdominal pain or headache occurs occasionally. In the pharynx are noted grayish-white papulovesicular lesions which are about 1 to 2 mm. in diameter and have an erythematous base (figure 1). These lesions progress over a period of several days to form slightly larger ulcers which are usually found on the anterior pillars of the tonsils, and on the soft palate, uvula, or the tonsils themselves. The symptoms of herpangina persist for two or three days. The throat lesions are in evidence for four to six days after the onset of the illness. Febrile convulsions occur in a few cases, and some conjunctival congestion and a mild maculopapular rash are present in some cases. The disease predominantly affects children who are two to six years old.

Acute infectious (herpetic) gingivostomatitis is a common disease which occurs throughout the year and affects children of about the same age as those affected by herpangina. The usual symptoms, which include fever, dysphagia, sore mouth, fetor oris and bleeding gums, are relatively gradual in onset. The patient is moderately severely ill, and often

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has submandibular lymphadenopathy and hyperemia, hypertrophy and/or hemorrhage of the gingivae. Vesiculation or ulcers or both of these lesions commonly occur on the gums, tongue, lips and buccal mucous membrane (figure 2). Occasionally, such lesions occur on the anterior pillars and pharynx. The fever lasts for three or four days, although there may be some lingering elevation of temperature for virtually a week. The oral lesions persist for 8 to 12 or 14 days.

Thus it can be seen that these two diseases have certain features in common. They are both relatively common diseases of childhood which predominantly affect children who are between two and six years of age. They are both contagious diseases which often occur epidemically in several members of a family or in several children in the same neighborhood. They both cause relatively high fever with at least a few days of general malaise, and they both cause lesions of the mucous membrane of the oropharynx which are originally vesicular but progress to ulceration.

Despite these similarities, it is possible with fair certainty to differentiate clinically between herpangina and herpetic gingivostomatitis. The site of the lesions is probably the most useful differential point. The presence of ulcers on the gums, lips, tongue or buccal mucous membrane, or gingival hyperemia and hemorrhage denotes infectious gingivostomatitis. The presence of lesions which are limited to the anterior pillar or soft palate denotes herpangina. However, it should be noted that lesions do occur on the anterior pillars and soft palate in some cases of herpes simplex infection, and the careful clinician will not accept such a location of lesions as being diagnostic of herpangina until he has searched the entire mouth for ulceration.

Another differential point of some importance when one first sees a patient is the fact that most patients with infectious gingivostomatitis have submandibular lymphadenopathy, which rarely occurs in cases of herpangina. At least in the northern climate, it is helpful to know that herpangina occurs only during the summer and that herpetic infection may occur throughout the year. The duration of oropha-

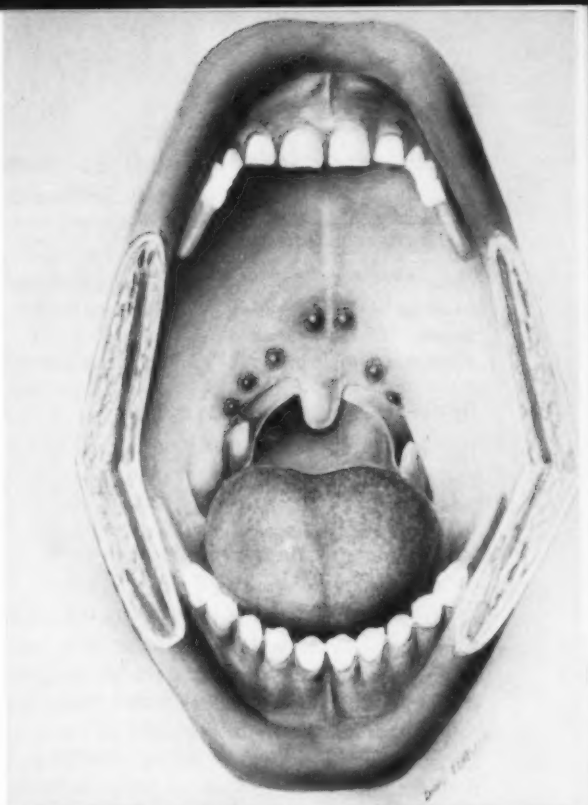

FIGURE 1. Herpangina.

FIGURE 2. Herpetic gingivostomatitis.

TABLE 1

DIFFERENTIAL FEATURES OF HERPANGINA AND HERPES SIMPLEX GINGIVOSTOMATITIS

DIFFERENTIAL FEATURES	HERPANGINA	HERPES SIMPLEX GINGIVOSTOMATITIS
Cause	Group A Coxsackie virus	Herpes simplex virus
Usual age of affected children	Two to six years	Two to six years
Season	Summer	All year
Site of ulcerative lesions	Anterior pillars, soft palate and fauces	Gingivae, tongue, lips, buccal mucosa; rare on anterior pillars and pharynx
Gingival involvement	None	Hyperemia, hypertrophy and hemorrhage
Duration of fever	2 to 3 days	3 to 7 days
Duration of lesions	4 to 6 days	8 to 14 days
Fetor oris	Rare	Usual
Submandibular lymphadenopathy	Rare	Usual

ryngeal lesions may aid in the differentiation retrospectively if it is recognized that such lesions are present in patients with gingivostomatitis for 8 to 14 days, while they are present for only four to six days in cases of herpangina. In general, it might also be said that the ulcerative lesions of herpetic infection become somewhat larger and deeper than do those of herpangina. A markedly fetid odor is usually present on the breath of patients with herpetic gingivostomatitis, but not on the breath of those with herpangina.

Routine laboratory tests are of no value in distinguishing herpangina from gingivostomatitis. In cases of either disease the initial leukocyte count is essentially normal, but there is a slight tendency toward diminution in total count and an increase in the relative number of lymphocytes as the illnesses progress. Throat and mouth cultures for bacteria reveal an essentially normal flora. *Candida albicans* have been found in cases of both diseases in an incidence slightly greater than that considered normal, but there has been no diagnostic abundance of either fusiform bacilli or spirochetes in the mouth or throat.

While it is not to be expected that the clinician would need to employ a virus laboratory to complete his clinical diagnosis in cases in which fever is associated with oropharyngeal lesions, the clinical differentiation between herpangina and herpetic gingivostomatitis has been confirmed in several studies which included virus diagnostic technics. The virus differentiation can be completed by employing infant Swiss mice as the host. When specimens of throat material or fecal material obtained from patients with herpangina are injected into suckling mice, they cause symptoms which are typical of infection with group A Coxsackie viruses, namely, flaccid paralysis of the extremities of the mice. When these symptoms occur in the mice, a suspension of the body of affected animals is employed in further identification and typing for strain specificity with standard Coxsackie antisera.

When specimens of saliva of patients with infectious gingivostomatitis are injected into young mice, they cause symptoms suggestive of herpes simplex infection, namely, weakness, abdominal distention, and spastic paralysis of the hind limbs of the mice. Material obtained from animals so affected is identified by means of neutralization tests with rabbit serum prepared from stock strains of herpes simplex. It should be recalled that laboratory diagnosis of herpes simplex infection more traditionally is made by using rabbit cornea, embryonated hen's egg or adult mice as the host. Both neutralization and complement fixation tests for Coxsackie viruses and herpes simplex virus may be carried out with serum obtained from a patient early in his illness and again during convalescence. The importance of including such serologic tests to show a rise in the titer of specific antibodies present during the course of an illness is emphasized by the knowledge that certain per-

sons may merely be carriers of Coxsackie and herpes simplex viruses. Thus, merely isolating the virus from their secretions does not establish that they are currently undergoing an infection with the microbiologic agent.

Although those engaged in these studies feel that it should be possible in most instances to differentiate between herpangina and herpetic gingivostomatitis without laboratory assistance, there are a few known instances in which these diseases occurred concurrently and produced a clinical picture characteristic of both diseases. This probability should not be forgotten in dealing with etiologic agents as prevalent as those causing these diseases.

The ability to differentiate these two common diseases of childhood is of practical importance in regard to both prognosis and therapy. For example, herpangina, although frightening in its sudden onset, is generally milder and of shorter duration than infectious gingivostomatitis, and therapy usually entails little other than reassurance and the administration of antipyretics. The extent and duration of the lesions, including gingival involvement, in cases of herpetic infection may necessitate the use of local analgesia, antisepsis and hemostasis. At times, it is also necessary to employ parenteral fluid therapy.

Probably as important as being able to differentiate these two diseases is to recognize that they are clinical entities, that their cause is known, that their prognosis is well established, and that therapy does not necessitate the use of antibiotics. There is no evidence that antibiotics have been of benefit in the treatment of patients with either of these diseases. In fact, theoretical observation and experience in several cases would lead me to say that the use of antibiotics should be avoided in cases of herpangina or herpetic gingivostomatitis, first, because they do not help, and, second, because they may allow an overgrowth of *C. albicans* and other antibiotic-resistant organisms to the eventual detriment of the patient.

Postgraduate Clinical NOTES

34. CARE OF THE TEETH

According to records of business income, a total of $1,600,000,000 was spent during the year ending July 1, 1953 in the United States for dental care. . . . This figure represents 15.6 per cent of the total annual expenditure for medical care of all types, including health insurance, hospitalization, nursing, etc. Unquestionably, this represents a greater financial outlay by the American nation for dental care than for any other medical specialty.

P. J. Brekhus, *Journal of the American Dental Association*, 48:347, 1954

Errors in Fluid Therapy for Children

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PHYSICIANS are called on to administer fluids parenterally to children in cases in which fluids are lost in excess or when the intake is inadequate. Fluid therapy ideally should replace requirements, deficits and current losses, and should return the patient to an electrolyte and water balance.[1] We periodically see in children errors in fluid therapy which are easily avoidable by combining a few simple principles with a few simple calculations.

Recently, modifications of parenteral administration of fluids have been developed to get rapid repair. However, most of one's fluid problems do not require such intracellular ions as magnesium and phosphorus, and these and other variations will not be discussed. Mistakes are made even with the common solutions.

L. A. BARNESS

PAUL GYÖRGY

Overhydration

The worst and most frequently made error is to administer fluids too rapidly. This results in either overhydration with peripheral edema, or pulmonary edema, cardiac decompensation and death.

Tables 1 and 2 show the management of fluid therapy when the laboratory is unavailable or before laboratory reports are returned. For the rarer, more complicated fluid replacement problem, the laboratory is vital and the calculations are made on the basis of laboratory reports and patient response. The usual laboratory studies recommended are serum chloride, serum carbon dioxide, serum sodium, serum potassium, serum urea nitrogen and stool culture.

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TABLE 1

PARENTERAL ADMINISTRATION OF FLUIDS FOR MODERATE DEHYDRATION

WEIGHT OF CHILD, POUNDS	MILLILITERS GIVEN DAILY PER POUND OF WEIGHT	DAY
Under 15	100	First
	75	Second
	60 to 75	After the third
15 to 25	75	First
	50 to 75	After the second
25 to 40	60	First
	40 to 60	After the second
Over 40	30 to 40	

One-fourth or one-half of the fluid should be given in the form of physiologic saline solution or as another solution containing an equivalent amount of sodium chloride. Ten milliliters per pound of blood can be given daily. Blood contains an equivalent amount of sodium chloride.

If acidosis is present, one-half of the total saline equivalent can be given as a sixth-molar solution of sodium lactate or a sixth-molar solution of sodium bicarbonate. Beginning on the second day, 1 or 2 mEq. of potassium per pound of weight should be given if the patient is voiding.

For maintenance, for example, in the postoperative treatment of patients who have not lost fluid, one may use one-half to two-thirds of the stated quantities of fluid and the same proportion of electrolytes.

TABLE 2

COMPOSITION OF PARENTERAL FLUIDS FOR MODERATE DEHYDRATION*

WEIGHT OF CHILD, POUNDS		Na+, mEq.	Cl—, mEq.	LACTATE, mEq.	MAXIMAL WATER *(ml.)*	BLOOD OR PLASMA *(ml.)*
Under 15	(a)	6	6		100	
	(b)	6	3	3	100	
	(c)	5	2.5	2.5	90	10
15 to 25	(a)	4.5	4.5		75	
	(b)	4.5	2.7	2.7	75	
	(c)	4.0	2.0	2.0	65	10
25 to 40	(a)	3.6	3.6		60	
	(b)	3.6	1.8	1.8	60	
	(c)	3.0	1.5	1.5	50	10
Over 40	(a)	2.4 to 3.6	2.4 to 3.6		40 to 60	
	(b)	2.4 to 3.6	1.2 to 1.8	1.2 to 1.8	40 to 60	
	(c)	2.0 to 3.0	1.2	1.2	40 to 60	10

*The figures represent the amounts per pound of body weight which should be given in 24 hours.

For maintenance, one-half to two-thirds of these amounts should be given, and the proportion of electrolytes should be the same.

When a patient is in shock, one can run the first fluids in as rapidly as desired. For example, for a 10 lb. child with severe diarrhea we might start with 50 ml. of a 10 per cent solution of dextrose while blood is being cross matched; rinse the tubing with 25 ml. of physiologic saline solution, add 100 ml. of blood (10 ml. per pound) and rinse the tubing with 25 ml. of saline solution. Since we had calculated that this child, in 24 hours, needed 10 lb. x 100 ml. per pound = 1000 ml. of fluid, of which one-half, or 500 ml., can be physiologic saline solution or its equivalent, we have remaining to run in during this first 24 hours 1000 — (50 + 25 + 100 + 25) = 800 ml. of the total remaining fluid; 500 — (25 + 100 + 25) = 350 ml. of the total remaining saline equivalent. If the patient is acidotic, we would give half of the saline equivalent, 250 ml., as a sixth-molar

lactate solution. Therefore, after the first 200 ml. were run in, the remaining 800 ml. would consist of: 250 ml. of a sixth-molar sodium lactate solution, 100 ml. of physiologic saline solution and 450 ml. of 10 per cent solution of dextrose in distilled water.

These three solutions would be mixed together to prevent too rapid changes in the chemical composition of the serum, and would be run in at the rate: 800 ÷ 24 = about 33 ml. per hour = 10 drops per minute.

This is a usual safe rate. Of course, no one starts an intravenous infusion and lets the patient remain unattended for 24 hours, and then recalculates for the next 24 hours. Whenever an infusion is being given, the patient should be checked frequently, and if he is in distress, the infusion should be slowed or stopped. Or, if the desired result is not being obtained, the rate may be increased slightly.

Another warning about overhydration is useful for those patients with chest disease, intracranial disease or anemia. These patients should receive no more than one-third to one-half the amounts of fluid, blood, and electrolyte solutions stated, and these must be given slowly and carefully. It always should be remembered that adding hyaluronidase to a solution that is being infused subcutaneously indicates that the solution will be absorbed at close to the same rate as one that is infused intravenously, and the same care should be taken with such a clysis.

Postacidotic Tetany

A not too uncommon occurrence is seen in children who are recovering from acidosis.[2] These children, after correction has started, become hyperirritable due to hypocalcemia. Five to 10 ml. of a 10 per cent solution of calcium gluconate given *intravenously* over at least a 5 to 10 minute period will correct this condition.

Underhydration

Some children, either with diarrhea, diabetes, heat stroke, pyloric stenosis, persistent vomiting, surgical drainage, or before or after operation, are simply not given fluids, or are given inadequate fluids. All these children will eventually become acidotic, go into shock, and die. If they happen to have added infection, antibiotics will not reach the site of infection. Fluids given as described above will alleviate this state.

Attempts at Hydration with Isotonic Saline Solutions

In such states as diabetes or heat exhaustion, relatively large amounts of salt are lost as compared to the water loss. In such cases, fluid replacement can be in the form of physiologic saline solution. Diabetic coma is an exception in other ways to fluid problems. While all the initial fluid may be isotonic saline solution, the acidosis is usually severe and requires sixth-molar solution of sodium bicarbonate for correction. Initially, one-fourth of the total amount of fluid to be given can be in the form of sodium bicarbonate solution. Later, when the chemical composition of the serum has returned to normal, the base can be modified. However, this type of dehydration is relatively rare compared to some of the other parenteral fluid problems.

It is now well known that rehydration occurs, except with marked salt loss, much more easily and quickly when solutions are given which contain less salt than does physiologic saline.[3] Also, severe potassium deficiency can occur when physiologic saline solution is used. Therefore, for usual replacement, not more than one-fourth to one-half of the total amount of fluid should be given as physiologic saline solution. Failure of an adequate response when adequate total fluid is used is frequently due to use of physiologic saline solution.

Attempts at Hydration with Dextrose Solutions; Water Intoxication

Occasionally the pediatrician, and frequently the surgeon, will attempt to maintain hydration with dextrose solution in the mistaken belief that physiologic saline solution will make the incisional site edematous. While it is true that immediately after operation a patient will tend to retain salt, nothing makes a wound swell as much as improper composition of the fluid and improper rates of administration.

This danger, however, is minor compared with a much more serious danger of low-salt infusions. As dextrose solution is given, salt is washed out by the kidney and the circulating solutions become hypotonic with respect to the cells. To maintain osmotic equilibrium, the cells imbibe water and enlarge. The most frequent sites of trauma due to this improper therapy are the brain, where cerebral edema occurs, manifested by convulsions, or the kidney, where anuria follows.

If prevention is not practiced by using the fluids as described, treatment consists of slow infusion of physiologic saline solution or 2 to 3 per cent solution of chloride until the convulsion has ceased, or until 50 ml. has been given.

If surgical drainage is necessary, in addition to the fluids already described for maintenance, special fluids[4] should be added to replace, cubic centimeter for cubic centimeter, the fluids lost by drainage.*

Potassium Deficits

Potassium deficits have recently been described.[5] In summary, it is recommended to start the use of potassium on the second day of parenteral therapy if solutions are not given orally. Potassium levels may be checked by the electrocardiogram or by a flame photometer. Potassium deficiency manifests itself by weakness, ileus, and, finally, by heart failure. We give a minimum of 1 mEq. and a maximum of 2 mEq. of potassium, as potassium chloride, per pound per day, starting on the second day, to all patients maintained by parenteral therapy.

Oral Administration of Fluids

Part or all of the fluids may be administered orally if the condition of the patient warrants. In general, one need not calculate as accurately when fluids are administered orally. The same general precautions, however, are necessary. One cannot give all dextrose and water, or water intoxication will occur; nor can one use only physiologic saline solution, or edema will follow. Likewise, some children, especially those with poor kidney function, are likely to drink too much fluid and become overhydrated.

Summary

Fluid therapy for children is simple. Only a few calculations, a few basic principles, and careful watching are necessary. If these are remembered, pitfalls such as overhydration, pulmonary edema, cardiac failure, underhydration, shock, postacidotic tetany, further dehydration and water intoxication will be avoided.

*The composition of these special fluids is as follows:[4]

Fluid used with gastric drainage:	
Potassium	17 mEq.
Sodium	63 mEq.
Ammonium	70 mEq.
Chloride	150 mEq.
Fluid used with intestinal drainage:	
Potassium	12 mEq.
Sodium	138 mEq.
Lactate	50 mEq.
Chloride	100 mEq.

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Scientific Exhibit

Nonrachitic or Physiologic Bowing

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FIGURE 1. Nonrachitic bowing at peak of deformity. Boy, 24 months old, in fourteenth month of bowing. Girl, 14 months old, nine months after "onset." The children are not siblings.

FIGURE 2. Same boy shown in figure 1, five years later. He received no treatment in the time following the first photograph.

Adapted from an exhibit prepared in the Department of Illustration of Vanderbilt University School of Medicine, by Susan H. Wilkes, Lewis D. Nichols and Philip E. Givan, and presented at the 1954 meetings of the Southern Medical Association at St. Louis and the American Academy of Pediatrics at Chicago.

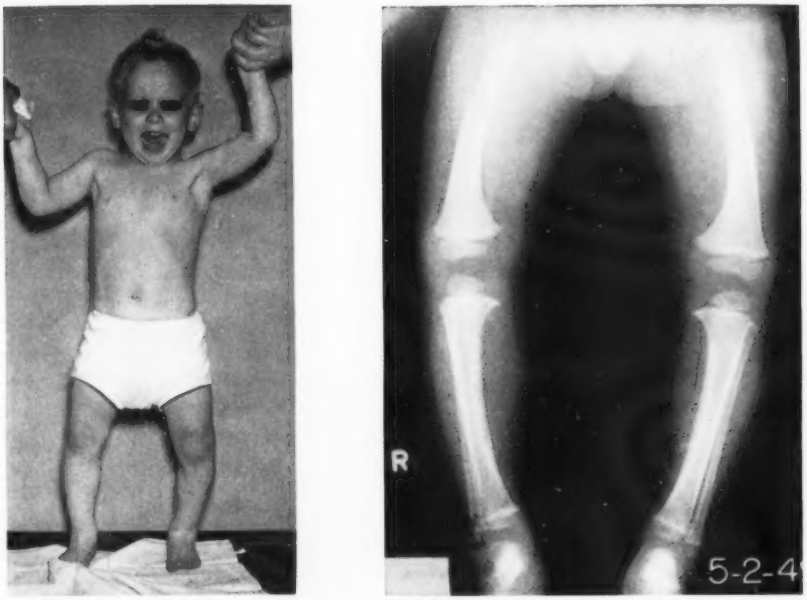

FIGURE 3. Typical nonrachitic bowing in a two year old boy.

FIGURE 4. Same child as shown in figure 3, four years later. He was treated with Dennis Browne splint for one month in the second year of deformity. Bowing was of four years' duration.

Nonrachitic or Physiologic Bowing

(continued)

FIGURE 5. Nonrachitic bowing in a 14 month old girl.

FIGURE 6. Same girl shown in figure 5, at eight years of age. She had received no treatment.

Physiologic Bowing Versus Rickets

	PHYSIOLOGIC BOWING	RICKETS
Age first noted	6 to 12 months	4 to 24 months
General health	Excellent	Poor
Dietary history	Adequate	Poor
Site	Regional or local; often asymmetric	Generalized symmetric
X-RAY FINDINGS		
Metaphysis	Medial "beak" with tibial angulation	Widened or flared; poor calcification
Tibial shaft	Normal density; straight	Poor calcification; actual bending
Epiphysis	Wedging	Broadened; symmetric but mottled
BLOOD CHEMISTRIES		
Calcium	Normal (9 to 11 mg. per cent)	Normal or decreased
Phosphorus	Normal (4 to 6.5 mg. per cent)	Decreased
Alkaline phosphatase	Normal (5 to 14.5 B. units)	Increased

FIGURE 7a. Nonrachitic bowing in absence of apparent aseptic necrosis of the medial tibial condyle. Epiphysial wedging, medial cortical thickening and tibial angulation are present. The bowing had not reached its peak.

FIGURE 7b. Two and a half years later when patient was clinically knock-kneed. He received no treatment.

FIGURE 8a. Bowing two months after "onset" which began at 16 months. A small area of metaphysial rarefaction prompted the diagnosis of Blount's disease. Epiphysial wedging, tibial angulation and medial cortical thickening complete the picture.

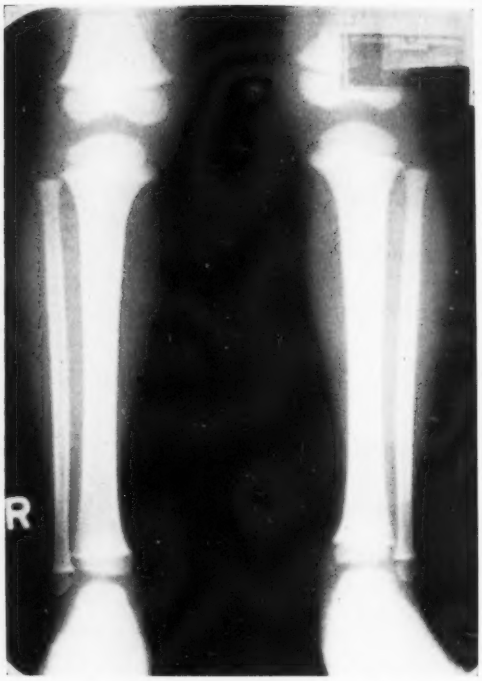

FIGURE 8b. The same legs 18 months later. The child had received no treatment.

FIGURE 9a. At 18 months.

FIGURE 9b. At three years.

FIGURES 10, 11 and 12. Sitting and sleeping positions habitually employed.

POSSIBLE FACTORS IN THE EXAGGERATION OF PHYSIOLOGIC BOWING

24 Cases of Nonrachitic Bowing

Sex incidence	
Male	13
Female	11
Familial tendency	3
Adequate vitamin D intake	20
Overweight	4
X-rays	
"Blount's disease"	9
"Nonrachitic bowing"	14
Stigmata of rickets	0
Nutritional state good	24
Blood chemistries (normal)	13

12 Cases of Nonrachitic Bowing
(Follow-up)

Age of onset (average age: 11 months)	
Noted at walking	9
Noted before six months	3
Treated by orthopedic clinics	
Total	5
Increased vitamin D	3
Appliances abandoned	4
Cases untreated	7

CONCLUSIONS

1. The bowing is a physiologic variant influenced by certain postural factors.
2. The condition is not associated with biochemical or roentgenographic rickets.
3. The bowing tends to regress spontaneously and in most cases deserves conservative management.

Regional Ileitis and Ileocolitis

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ALTHOUGH nonspecific granulomas of the gastrointestinal tract had been recognized for a long time, it was not until 1932 that Crohn, Oppenheimer and Ginzburg[1] isolated a subgroup, regional ileitis, and described its pathologic changes, symptoms and surgical treatment. Since this communication, another important observation has been made, namely, that the granulomatous process may involve almost any segment of the small intestine, often together with portions of the colon. The cecum and the terminal portion of the ileum are most frequently involved. No cause has been definitely proved although many agents or pathologic conditions have been suspected, such as specific bacteria, Protozoa, bacillary dysentery, viruses, sarcoidosis, trauma and hereditary factors. The pathogenesis, too, is uncertain, although some ascribe the disease to vascular changes, others to lymphatic block.

Regional ileitis is characterized by a submucous chronic necrotizing and cicatrizing inflammation. The disease seems to have a predilection for the ileum and may end there abruptly. However, it may involve the bowel segmentally anywhere from the duodenojejunal angle, or it may occasionally affect the entire small intestine. Grossly, the serosa of the bowel is red, congested, and often covered with exudate, and the walls are usually edematous, thickened and leathery. The bowel itself may be dilated or definitely stenotic. While various segments of the intestine may be grossly involved and are known as skip areas, microscopic disease may still be present in grossly normal bowel. The corresponding mesentery is usually hard and rigid, and the inflamed lymph nodes are definitely enlarged. The mucosa has a cobblestone appearance, and is crossed by linear ulcers, usually parallel to, and most frequently along the mesenteric border. These ulcers often penetrate the mesentery. The microscopic appearance, which is not pathognomonic, consists of acute, subacute or chronic inflammation. The earliest lesions are apparent in the submucosa, and

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giant cells are invariably present.

Fistulas are characteristic of ileitis. They may form between the intestine and adjacent viscera, such as the large bowel, bladder, uterus, fallopian tubes or vagina. A fistula to the anterior abdominal wall may develop subsequent to either an appendectomy or the spontaneous rupture of an abscess from an unrecognized ileitis. More rarely, the abscesses may point in the inguinal or the lumbar region. Rectal or rectovaginal fistulas, which are quite common, may result from the devious tracting of infection from the small intestine. It should also be remembered, however, that the diarrhea, which is frequent, may cause an infection of the crypts of Morgagni and result in ischiorectal fistulas.

Clinically, the patients give a history of general malaise, anorexia, loss of weight, easy fatigability, diarrhea, and fistulas about the rectum. As the diarrhea increases, colicky abdominal pain develops, and, occasionally, intermittent intestinal obstruction. Mild fever is usually present. At this stage, the diagnosis may be suspected. More rarely, the first intimation of the disease may be a severe melena, or the appearance of a cloudy urine containing pus, or a foul vaginal discharge. Physical examination may disclose, in addition to anemia, loss of weight and low grade fever, external fistulas or an abdominal mass. The mass is usually in the right lower quadrant, but its site and size vary as do the external openings of sinuses and fistulas. Occasionally, an inflamed segment of bowel may be felt through the rectum or vagina.

Roentgenologic Findings

The roentgenologic findings are rather characteristic. Initially, roentgenologic examination of the small intestine may reveal only an alteration of the mucous membrane pattern of the ileum. Subsequently, one of the most common findings is the presence of the string sign in the terminal portion of the ileum. This is due to narrowing of the lumen of the bowel by spasm and scar tissue formation. The segmental character of the lesions produces skip areas, the dilatation representing normal bowel alternating with areas of disease. Intra-abdominal fistulas, characteristic of ileitis, frequently can be demonstrated.

The cecum may be spastic and frequently irregular owing to swelling of the terminal portion of the ileum pressing upon the valve of Bauhin. However, the entire large bowel should always be examined for evidence of segmental colitis.

Diagnosis

This as a rule is not difficult. Diarrhea, anemia, abdominal cramps, fever and the presence of a mass or fistula, with or without any positive roentgenologic findings, usually are sufficient to permit one to make the diagnosis. However, the disease must be distinguished from amebic dysentery, idiopathic colitis, abdominal Hodgkin's disease, lymphosarcoma and sarcoidosis, as well as from tuberculosis.

Treatment

Once the diagnosis has been made, the question arises as to the best method of treatment. Patients should be treated conservatively unless loss of weight, debilitating diarrhea, cramps, fever, masses, intermittent intestinal obstruction and fistula transformation are present. Occasionally, the disease may either remain stationary or disappear, and even diffuse jejuno-ileitis has been known to vanish. During the period of observation, roentgenologic studies should be made frequently.

There is no specific medical therapy except the usual supportive treatment consisting of rest, a high protein diet, vitamins and blood transfusions. The antibiotics and cortisone are of dubious value. However, if the patient shows no evidence of improvement, operation is not only advisable but mandatory. Prior to operation, appropriate fluids should be given parenterally. The usual bowel preparation with antibiotics is prescribed, but cathartics are carefully given. The fact that intestinal loops are often obstructed and matted together makes intestinal intubation advisable. This should be done at least 48 hours before operation. Not only does it effectually decompress the intestine but the normal bowel usually becomes accordion pleated, making it easy to handle. The tip of the tube which points dis-

tally eliminates the necessity of mechanically tracing the bowel in order to determine the direction of the intestinal flow.

Spinal anesthesia is employed routinely. The incision is usually a lower right rectus muscle-splitting incision unless roentgenologic examination reveals isolated pathologic changes high in the left upper quadrant. The entire bowel is examined. The extent of the disease is estimated, and the presence of fistulas noted. The question then arises as to whether a radical excision or simple sidetracking of the diseased segments should be performed. Originally, I routinely resected the diseased ileum and part of the colon and restored the continuity by a side-to-side ileotransverse colostomy. The mortality was appreciable. In an attempt to lower it, a two stage operation was suggested. At the primary stage, an ileocolostomy with exclusion was done, and the resection was performed later. However, after the first stage, the clinical improvement was usually so marked and disappearance of the inflammatory mass and cutaneous fistula so rapid that I felt that resection could be postponed indefinitely. In 1939, Ginzburg, Sussman and I[2] reported 19 cases in which a satisfactory result was obtained by using this simple procedure rather than resection.

There have been objections to ileocolostomy with exclusion. The fear that sufficient back pressure might endanger the suture line of the distal excluded ileum has not been substantiated. It was also felt that in cases in which ileosigmoidostomy was performed the emptying of the fluid contents of the ileum might irritate the sigmoid and rectum, and produce diarrhea. This has not been observed in any case in which the sigmoid was found to be normal at the time of operation. As a matter of record, the diarrhea which was previously present has disappeared in cases of right-sided colitis and ileitis. In a number of instances, previously discharging perianal fistulas healed instead of becoming aggravated. It has also been stated that ulceration might result from stasis and retention in the excluded loop of colon. This too has not been encountered. Retrograde peristalsis is present in the colon normally, and, when an impulse is received distally, the colon usually responds by emptying itself in the normal direction.

In a number of instances postoperative studies were made with a barium enema. These showed no abnormal dilatation or distention of the excluded colon, and the haustrations and sacculations were normal even after years of unilateral exclusion. When a barium enema is administered, there is, as a rule, retrograde passage through the ileocolic stoma as well as into the excluded bowel. However, the force of barium enema is sufficient to carry the contrast medium to a point much farther proximal into the diseased segment than occurs ordinarily by retrograde peristalsis. Therefore, in cases of regional ileitis, ileotransverse colostomy with exclusion has been my procedure of choice since 1939. (In instances in which the disease is localized to the jejunum, resection with end-to-end anastomosis has been found to be quite satisfactory.) In cases of ileocolitis mainly confined to the right side of the colon, an ileosigmoidostomy with ileal division is performed. There are cases, however, especially those in which multiple fistulas are present and cannot be effectively excluded, in which the disease is often so extensive that resection must be done even in the face of a higher mortality.

After either resection or sidetracking, the abdomen is closed without drainage. The long intestinal tube is retained until peristalsis returns, as evidenced by the passage of gas and feces by rectum. The average mortality rate for resection is 11.2 per cent; that for sidetracking, 4.6 per cent.[3]

Postoperatively, most of the patients have a good appetite and gain weight. Within a reasonable length of time, the feces become soft in consistency, and the bowel movements occur about three times a day and without cramps. While many patients remain well, there is a return of symptoms similar to the original disease in many, and roentgenologic examination confirms a persistence of recurrence of the ileal disease usually in the area of the stoma.

The persistence, progression or recurrence of disease after operation for nonspecific

granulomatous ileitis is more frequent than was originally reported. It would seem that the incidence of further disease will increase in direct proportion to the length of time that the patients are followed. The recurrence rate was 28.9 per cent in 781 cases in which a simple exclusion operation was performed and 21.8 per cent in 2,209 cases in which resection was performed.[3] The type of surgical procedure, therefore, appears to have little influence on the ultimate course of the disease. Clinical experience seems to indicate that the fate of the patient depends on whether or not the disease is definitely localized and remains localized to a comparatively small segment of bowel, preferably the terminal portion of the ileum which has been completely resected, or completely sidetracked.

I have stressed the importance of recognizing skip areas, but unfortunately, as has been stated, these areas of incipient disease cannot always be recognized at the time of operation because the mucosal or submucosal lesions are often so small that they defy manual or visual detection. That these microscopic areas of ulceration are present and unrecognized has been proved by a biopsy of the bowel, presumably normal, which was used for anastomosis to the colon. In a recent case of extensive ileitis in which the patient was a 19 year old girl, the intestine was excluded 45 cm. proximal to the last visible evidence of disease. A section of the ileum taken at the point of anastomosis revealed microscopic evidence of acute and chronic granulomatous changes. These foci are the usual basis for further extension and progression of the disease in the proximal portion of the ileum. The incidence of recurrence in the proximal portion of the ileum, therefore, may be diminished, though probably never eliminated, by routinely defunctionalizing the ileum at a point at least 60 cm. proximal to the last point of gross evidence of the disease, a distance which is greater than that generally advocated.

There are many cases in which activation of the disease occurs many years after primary operation. In such cases, it is unlikely that the skip areas have remained dormant during the long symptom-free interval. It would appear more logical to postulate that the unknown etiologic agent which originally caused the disease may again have become activated. The presence of an active or dormant lesion in an excluded distal portion of the ileum probably plays no part in this type of recurrence. It is unlikely that the defunctionalized bowel acts as a focus from which the disease can travel via the mesenteric lymph vessels to involve the proximal bowel at or near the site of the enterocolostomy. Postmortem examination and exploratory inspection of the excluded ileum at secondary operations indubitably support this contention. As a rule, the pathologic process in the defunctionalized bowel has undergone regression after complete diversion of the fecal current.

On the other hand, it cannot be denied that persistence of disease in an excluded ileum does occur rarely. In such cases, further ulceration from areas of disease in the sidetracked ileum may lead to fistulous communications with other intestinal loops, the sigmoid and rectum. This is a serious and often lethal complication of enterocolostomy with exclusion and one of the more potent arguments in favor of primary resection in all cases. Nevertheless, I do not believe that these unusual instances of persistence of disease in the excluded ileum condemn ileocolostomy with exclusion. Moreover, resection of the right side of the colon and excluded ileum may be done as a second stage procedure if necessary, with a lower mortality rate.

The problem of recurrent ileitis, then, is the treatment of the disease usually in the proximal portion of the small bowel, and more rarely in the excluded ileum. In the latter case, the defunctionalized ileum and as much of the colon as necessary are resected.

In cases in which there is a recurrence in the proximal portion of the ileum, after either resection or exclusion, and in which an ileotransverse colostomy has been performed, a second ileal division with an ileosigmoidostomy offers a conservative solution to a complicated problem in which radical operation may become extremely hazardous. It may be technically difficult to take down a previous anastomosis and to separate edematous friable

bowel from other viscera. Resection of this type of intestine with its thickened, edematous, gland-bearing mesentery often produces shock.

A follow-up study has disclosed that rather satisfactory results were obtained in a group of cases in which a secondary exclusion operation was performed. Some of the patients, particularly during periods of emotional upset, have had frequent bowel movements, but not to a disturbing degree. No symptoms have developed thus far which could be attributed to the presence of the isolated ileal loop which was left attached to the transverse colon. There is ample evidence that the disease in the defunctionalized bowel regresses to much the same extent as it does in the primary excluded ileum. In one case the patient died two and a half years after secondary ileosigmoidostomy with ileal division for recurrent ileitis following a primary resection with ileotransverse colostomy. Autopsy revealed that the excluded bowel, which measured 27 cm. in length from the point of anastomosis to the transverse colon, was grossly normal and that there was no further evidence of the disease. In another case the patient entered the hospital because of an intestinal obstruction three months after a secondary ileosigmoidostomy with ileal division for proximal recurrence. Exploration disclosed that the acutely inflamed bowel which had been previously excluded was normal in appearance. A barium enema given to another patient two months after a secondary exclusion revealed that the local inflammation at the region of the ileotransverse colostomy had subsided.

The duration of the symptom-free interval after primary operation for ileitis can be surprisingly long. This is illustrated by cases in which the patients remained well for more than 14 years before a recurrence was manifested clinically. Freedom from symptoms does not necessarily mean eradication of disease. In one case, recurrence was demonstrated by roentgenologic examination after nine years of complete well-being. Despite this, the patient remained clinically well for five more years. In another case, persistent disease in an excluded loop was eradicated by resection after 12 symptom-free years. This procedure was followed by an asymptomatic proximal recurrence which has lasted two years to date. There is one case which deserves special mention. The patient had all the complications of regional ileitis, namely, peritonitis, intestinal obstruction, abdominal mass and fecal fistula. In six years he underwent seven major operations for his disease. A complete cure was obtained by a secondary ileal division with ileosigmoidostomy, and he has remained well for the past seven years.

The incidence of intestinal obstruction in cases of this disease is appallingly high. This is due to intrinsic bowel disease in some cases, and to adhesive bands in others.

Summary

Recurrent symptoms following either resection or exclusion for disease of the terminal portion of the ileum are not as rare as originally reported. The recurrence rate calculated from reports in the literature is above 20 per cent. The symptoms are due to a progression of the disease in the proximal portion of the ileum at or near the point of anastomosis to the transverse colon. Rarely are the symptoms due to a persistence of disease in the excluded ileum. The usual recurrence results from skip areas of incipient disease which are present in the proximal portion of the ileum at the time of anastomosis to the transverse colon. The symptoms, physical signs and roentgenologic findings in this type of recurrent ileitis are similar to those of the primary disease. In cases in which an ileotransverse colostomy has been performed, the treatment of choice is a secondary ileal division with ileosigmoidostomy. The point of ileal division should be at least 60 cm. proximal to the last visible diseased segment. It is advisable at all times at operation to obtain a bioptic specimen of the portion of the ileum which is to be used for anastomosis.

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Drug Therapy for Hypertension

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ARTERIAL hypertension in its primary form, that is, hypertensive vascular disease or essential vascular hypertension, represents the important type of hypertension since it comprises at least 90 per cent of cases in which there is a significant elevation of blood pressure. In contrast to the secondary form, which results from causes well recognized, it is a vascular disorder of complex and undetermined origin. From investigative studies, both clinical and experimental, it seems probable that various mechanisms—neurogenic, renal, endocrine, hormonal, vascular and others unknown—contribute components of varying magnitude in individual cases.

Since the cause is unknown and the underlying factors numerous and variable, there is little hope that a single drug or compound will be found to constitute a panacea for hypertension. In contemporary literature there is an incomplete agreement regarding necessity for treatment of most patients with hypertension because the process is commonly benign in form. Published observations on large series of cases indicate a respectable mortality at 8 to 10 year follow-up periods, the mortality rate rising with increasing grade severity of hypertension and with ascending levels of diastolic pressure. Antagonists point out the relative longevity frequently observed in cases of benign hypertension, and emphasize that vascular disease may progress in spite of appreciable reduction of blood pressure. Recorded survival rates following sympathectomy for hypertension indicate that this method of treatment was definitely superior to conventional medical therapy prior to the advent of the newer antihypertensive compounds, statistics for which are currently being compiled. Most clinicians agree that hypertension existing for long periods will lead to or accelerate the progression of vascular disease in some cases, even though vascular lesions may ad-

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vance independently of controlled hypertension in others.

No standards are available which by common agreement indicate the exact level of increased blood pressure for which aggressive therapy should be instituted. In fact, no general accord has been reached regarding what constitutes normal blood pressure in different age groups. Patients whose blood pressures frequently rise above 140/90 mm. Hg deserve watching; consistent diastolic pressures above 110 mm. Hg warrant more specific measures. Therapy becomes more intensive and important under such comparative conditions as a strong family history of hypertension, younger age of patient, higher diastolic pressure, more rapid progression of hypertensive disease, and greater degree of tissue alteration secondary to the hypertensive process. Full emphasis must be given to the necessity for treating the patient as a whole, not just his blood pressure. The hypertensive problem with its concomitant vascular and tissue changes in the vital areas, such as the brain, heart and kidney, should be attacked vigorously with every means at one's disposal, including rest, psychotherapy, drugs, diet and, when indicated, sympathectomy.

During the past several decades a wide variety of compounds have been utilized in treating hypertension, but most of these have been discarded for lack of general effectiveness. The ideal drug for widespread application to large groups of patients must be effective in lowering blood pressure on oral administration and be free of serious toxic and undesirable side effects. No drug at present fulfills these requirements.

Sedative drugs (phenobarbital, MEBARAL® and the bromides), the xanthine compounds (theobromine and theophylline and their salts) and the slow-acting nitrates (erythrityl tetranitrate and mannitol hexanitrate) are still widely used, but their hypotensive effects are mild and their clinical usefulness is limited. These sedative and vasodilating drugs are commonly employed together for older, tense, mild hypertensive patients, with variable results, often good.

The use of potassium thiocyanate was discarded but then was revived. Although it now is rarely employed, it still deserves a place in hypertensive therapy, particularly for younger patients who have severe, intractable headache. The concentration of thiocyanate in the blood must be followed in order to control oral therapy and to avoid serious toxic reactions, including an occasional death. The mode of action of the thiocyanate compounds is still unknown.

Recent investigative interest has centered on the utility of several new drugs extracted or synthesized during the past six years and the revival of one group long used for the treatment of toxemia of pregnancy.

Vasodepressor Agents

Veratrum compounds—For many years, extracts of *Veratrum viride* and *Veratrum album* have been employed for the treatment of hypertension accompanying the toxemias of pregnancy and their use for primary arterial hypertension recently has been revived. Most of these preparations represent crude or more purified mixtures of alkaloids derived from *Veratrum viride* (VERTAVIS®, VERATRONE®, VERILOID®, VERGITRYL® and UNITENSEN®). Considerable attention has been focused on the use of the pure alkaloids, protoveratrine A and B (VERALBA® and PROVELL MALEATE®) derived from *Veratrum album*. The action of these drugs is mediated through cardiovascular reflexes, and they cause central vasodepression and bradycardia. The bradycardia can be abolished by atropine, and the hypotensive effect may be relieved by ephedrine or phenylephrine hydrochloride.

These drugs have limited usefulness in the treatment of hypertension since the margin between the therapeutic and toxic effects is very narrow, and since nausea and vomiting frequently are induced before a significant fall in blood pressure is attained. Common side reactions include a feeling of choking, burning in the esophagus, nausea, vomiting, salivation and severe collapse, even though careful regulation of dosage is attempted. The hope originally expressed that the pure alkaloid, protoveratrine, would provide a wider margin between desired clinical response and toxicity has not been fulfilled clinically.

Although many drugs of the veratrum series are available for parenteral administration, extreme caution should attend their use intramuscularly or intravenously, since severe toxic effects may appear abruptly. Oral administration of the veratrum compounds alone is not satisfactory for hypertension, and they now are more widely used in combination with other drugs such as Rauwolfia and hydralazine. It would seem best for the physician to select one or two drugs from this group which may be administered orally or parenterally, and to obtain personal familiarity with their use. The dose and method of administration vary from compound to compound. In view of the common production of nausea when these drugs are administered orally, they should be given immediately after meals, and the dose should be increased gradually, since a single tablet may provide the difference between comfort and distress.

Dihydrogenated alkaloids of ergot—This group of drugs includes dihydroergocornine, dihydroergocristine and dihydroergokryptine, which now are combined as HYDERGINE®. They produce their primary hypotensive effect by central depression of vasomotor tone. They cause bradycardia, as do the veratrum compounds. Preliminary investigation has revealed that dihydroergocornine, when administered alone, produces a mild hypotensive action which tends to disappear after one month as tolerance develops. The combination of these compounds as Hydergine has not proved effective for hypertension, although increased cerebral blood flow and decreased cerebrovascular resistance have been observed.

Adrenergic Blocking Agents

In the past few years, a number of new compounds possessing antiadrenergic (adrenolytic and sympatholytic) action have received considerable investigative attention. The principal members of this group are piperoxan (benzodioxane, BENODAINE®, 933F), phentolamine (REGITINE®, C-7337), tolazoline (PRISCOLINE®), DIBENAMINE® and phenoxybenzamine (DIBENZYLINE®). These compounds act at the peripheral receptor areas to block the action of circulating adrenergic drugs and stimulation from the sympathetic nervous system. Intensity of blocking action varies from area to area, and complete blockade is not achieved.

Most of these drugs can be given both orally and parenterally. However, none are practical for the treatment of hypertensive disease since they fail to produce a significant depressor action when administered in therapeutic doses, and they induce serious unpleasant reactions, such as nasal congestion, nausea, vomiting, tachycardia and headache. All efforts to combine such drugs as Regitine or Dibenzyline with other compounds have not yet proved effective and satisfactory. When given alone, these drugs are quite disappointing in their hypotensive action. Currently, some members of this group have found usefulness in treating peripheral vascular disease and as diagnostic agents for pheochromocytoma, since they block the actions of both epinephrine and norepinephrine.

Anticholinergic Agents

The compounds of this group represent the most potent antihypertensive agents available today. They produce autonomic blockade, and block equally well the sympathetic and parasympathetic impulses at the ganglionic level. The blocking action is incomplete, and a full "chemical sympathectomy" is not attained.

Tetraethylammonium chloride—This was one of the first anticholinergic agents to be introduced. It lowers the blood pressure acutely when administered intravenously in doses of 400 mg. It is ineffective when administered orally, painful when given intramuscularly, fleeting in hypotensive action and, therefore, is impractical for use in the treatment of hypertension.

Hexamethonium and pentamethonium—Investigation of the pharmacologic properties of the methonium compounds (hexamethonium, C_6, and pentamethonium, C_5) has indicated that they have a potent anticholinergic action. The blocking action of hexamethonium has been considered superior to that of pentamethonium. Since these drugs block both the sympathetic and parasympathetic ganglia of

the autonomic nervous system, the principal hypotensive effects are mediated by blockade of the vasoconstrictor impulses in the sympathetic nervous system. The resulting decrease in the blood pressure, therefore, is greater when the patient is erect than it is when he is recumbent. These drugs cause many undesirable effects, such as blurring of vision, dryness of the mouth, constipation, ileus and atony of the bladder.

Investigation of the value of these drugs in the treatment of hypertension largely has been directed toward the use of hexamethonium chloride (BISTRIUM® chloride, ESOMID® chloride, HEXAMETON® chloride and METHIUM® chloride). This is a potent hypotensive agent; it is potentially hazardous, and it even may be lethal in cases in which such complications as encephalopathy and cardiac and renal insufficiency are present. Vascular thrombosis in the brain and heart and renal insufficiency have occurred in cases in which the blood pressure has been lowered too rapidly by the administration of this drug. It is most prudent to investigate the cardiac and renal status of the patient before the administration of this drug is started. Treatment with this drug should be initiated under controlled conditions in the hospital to observe the sensitivity to the drug, which varies in different cases.

The drug may be administered orally or parenterally. Absorption through the gastrointestinal tract is irregular and incomplete. I administer the drug parenterally only in cases in which severe hypertension is associated with vascular complications. Initially, 2 mg. of the drug is administered subcutaneously every four hours. The daily dose is increased until the desired effect is achieved. The interval between doses then is increased to six to eight hours if possible. A single dose of 50 mg. rarely should be exceeded, and a total dose of more than 300 mg. rarely should be administered in 24 hours.

One should be careful not to produce excessive hypotension, particularly orthostatic hypotension, and ileus and urinary retention should be avoided. Blood pressure sensitivity to small initial doses at the institution of therapy is commonly present even though tolerance to larger doses occurs later. Extreme recumbent hypotension may be combated with phenylephrine hydrochloride, and constipation with cascara, PROSTIGMINE® or URECHOLINE®. Low sodium diets apparently enhance the action of the methonium compounds. Oral absorption may vary in the same case from day to day and postural hypotension with excessive weakness and syncope may occur without warning. Impotency in young males, a serious complaint, is not easily avoided by omission of single or multiple doses before contemplation of intercourse.

After administration of the drug has been started, it should not be discontinued suddenly because this may cause a rapid deterioration in the patient's condition and death may occur, particularly in cases in which malignant hypertension is associated with lowered renal function. When the oral administration of hexamethonium is started, 125 mg. of the drug usually is administered before meals and at bedtime in order to spread the effect of the drug through the waking period and to permit more uniform absorption of the drug. Before each dose of the drug is administered, the blood pressure is determined with the patient in the standing and recumbent positions. The dose is increased daily, but care should be taken to avoid lowering the blood pressure too rapidly and to avoid cumulative effects of the drug. Two to 4 gm. per day usually constitute a satisfactory maintenance dose. This dose rarely should be exceeded. The ideal candidate for treatment with this drug would appear to be the younger patient who has progressive hypertension that is unresponsive to routine medical management and who presents conventional indications for sympathectomy. Older patients respond less well to this type of therapy, and the hazard of arterial thrombosis, particularly in the brain and heart, very probably is greater.

The hexamethonium salts are potent drugs in the management of hypertension. Wide fluctuations between recumbent hypertension and postural hypotension frequently prevent drug dosage sufficient to lower the supine blood pressure satisfactorily. A normal recumbent blood pressure is rarely obtained and a

compromise is generally made in the direction of partial rather than complete control. It has been suggested that the sitting blood pressure be lowered to near normal levels. The effects on systolic pressure are always greater than on diastolic pressure. Potential dangers are sufficient to necessitate caution even after extended experience.

Tolerance to the drug as measured by loss of effect on the blood pressure gradually develops in a matter of months in most cases. Hexamethonium poisoning, cerebral and cardiac complications, renal insufficiency and death have all been reported. Combinations of hexamethonium with hydralazine and Rauwolfia are regarded as more effective than any one of these compounds administered alone. In our experience, hexamethonium and hydralazine represent the most effective combination of drugs for the treatment of severe hypertensive disease, particularly if adequate time is reserved for careful titration of the dose of each drug.

Pentamethylene pyrrolidinium bitartrate (M&B 2050A, ANSOLYSEN®)—This new ganglionic blocking agent, resembling hexamethonium in action, has been synthesized recently and is reported to have less parasympathetic blocking effect than hexamethonium. Absorption from the gastrointestinal tract is more complete and uniform, less constipation is induced, hypotensive potency is five times greater and the duration of action is one to one and a half times that of hexamethonium. Oral administration of the drug generally is begun by giving 10 to 20 mg. three to four times daily, approximately six to eight hours apart. The daily dose is increased by 30 to 40 mg. until about 800 mg. is being given per day. Parenteral administration may be begun by giving 2 mg. every four hours. Each dose is increased by 2 to 4 mg. and the interval between doses is increased to six or eight hours, depending on the intensity and actual duration of the blood pressure response.

The indications and cautions are exactly the same as those outlined for hexamethonium. It is important to emphasize that if administration of the drug is discontinued suddenly it may lead to serious consequences, including a fatal hypertensive rebound. Although insufficient clinical experience has been gained with this drug, it seems to be equally as effective as hexamethonium.

Hydralazine

Hydralazine (1-hydrazinophthalazine, APRESOLINE®, C-5968) is a drug which has rather complex actions including a weak antiadrenergic effect, central and peripheral hypotensive action, and neutralization of pressor substances (angiotonin, pherentasin and serotonin). Other circulatory effects include increased cardiac output, tachycardia and an increase in renal blood flow while the blood pressure falls.

When administration of the drug is started, 10 mg. is given orally four times a day since larger initial doses commonly cause headache, nausea, vomiting and tachycardia. The dose often can be increased, preferably over a period of weeks, without appreciably increasing the undesirable effects. The maximal daily dose should not exceed 400 to 600 mg., but much larger doses have been given without causing significant reactions.

When this drug is used alone, it has a weak hypotensive action. It is contraindicated in cases of coronary insufficiency or congestive heart failure. Tolerance develops on prolonged administration. Additional unpleasant effects include nasal congestion due to its antihistaminase action, dizziness, paresthesia, tingling, and the occasional development of edema. The appearance of a "collagenlike" illness was observed in 8 to 13 per cent of cases in which the drug was being used. In most instances, the illness was mild in form, resembled rheumatoid arthritis, and disappeared promptly when administration of the drug was discontinued. However, in a few cases, the reaction was alarmingly severe and was manifested by fever, arthritis, pericarditis, pleuritis and L. E. cells in the blood, and thus simulated disseminated lupus erythematosus. ACTH and cortisone have been required to control this disturbing illness in a few cases. These reactions have occurred when larger doses, usually 400 mg. or more, of the drug have been given daily for relatively long peri-

ods of time, as long as five months or more.

Additional serious reactions to hydralazine have included a variable degree of bone marrow depression, pancytopenia and gastrointestinal bleeding. For these reasons it would seem wise to reserve large doses of hydralazine for the more severe hypertensive states in which mortality and morbidity overshadow potential dangers from the drug itself. In small doses the drug is not particularly effective but may be employed in various combinations with Rauwolfia preparations, Veriloid, protoveratrine and hexamethonium. When hexamethonium and hydralazine are used in combination, the administration of hexamethonium is begun first, and, as the blood pressure tends to fall significantly or to fluctuate widely, hydralazine is added.

Rauwolfia Serpentina

This drug, which recently was introduced in the United States for the treatment of hypertension, is derived from the root of an Indian plant, *Rauwolfia serpentina*. The available preparations are the powdered whole root (RAUDIXIN®), a partially purified alkaloidal mixture (RAUWILOID®, the alseroxylon fraction), and the pure alkaloid, reserpine (SERPASIL, RESERPOID and SANDRIL®), which is thought to be the active hypotensive principle derived from the crude preparation. The pure alkaloid, reserpine, is thought to possess 1000 times the hypotensive action, milligram for milligram, of the whole root. The pharmacologic action of preparations of Rauwolfia is incompletely understood. In some cases, the action on the brain produces a sedative quality described as drowsiness; in others, these drugs have a calming or tranquilizing effect, and, in a few cases, they cause a state of jitteryness with dreams, nightmares and even severe depression. The hypotensive action is probably centrally mediated. Parasympathetic stimulation produces bradycardia and tends to increase bowel function to the production of diarrhea in a few instances. The most common symptoms caused by the drug are fatigue, decrease in general energy, depression, nasal stuffiness which fails to respond satisfactorily to antihistaminics, increased appetite, and a gain in weight. No important differences in action have been noted between the use of impure mixtures and the pure alkaloid itself.

When the powdered whole root (Raudixin) is used, 50 mg. is given two to three times daily and the dose is increased if necessary until a total dose of approximately 500 mg. per day is given. When the active alkaloid, reserpine, is used, 0.1 to 0.25 mg. generally is administered two to three times daily. Since there is a slow cumulative effect of the drug over at least one to three weeks, the dose is increased gradually until 0.5 to 1 mg. is administered three times daily. Once the desired effects have been noted, additional increases in the dose do not produce further lowering of pressure and may increase side effects.

The drug seems most suitable in cases of mild labile hypertension in which the patients are tense, emotional and anxious. When administered alone it is not effective for the more severe forms of hypertension. It has been combined successfully with veratrum preparations, hydralazine and hexamethonium. When it is administered in this manner, its effects may be additive if not synergistic in relieving patients' symptoms and lowering blood pressure. The undesirable effects of the drug, notably fatigue, loss of energy and a feeling of depression, may be so great as to necessitate a considerable decrease in the dose or actual discontinuance of therapy. We have observed instances of rather severe depression in five patients who were being treated in this manner. The exact position of Rauwolfia in the cause of this reaction has not been proved but its etiologic role is strongly suspected. In general, Rauwolfia compounds are comparatively simple drugs to administer for hypertension since they are well tolerated in average doses. Complete freedom from danger has not yet been fully established.

Combinations of Drugs

The principle of combining drugs with different pharmacologic actions in order to attack the hypertensive process at separate points seems entirely acceptable. Each drug should be administered as a separate tablet in

nearly maximal tolerated doses before further drugs are added. When satisfactory hypotensive response is noted or when significant side effects occur, the dose may be reduced. Smaller yet effective doses of several drugs may be used in combination, and thus unpleasant or serious side reactions may be avoided. Multiple drugs in a single capsule or tablet are to be deplored, since the dose of one ingredient cannot be altered without changing the dose of others in the combination to levels which may not be desirable.

The most effective combination of drugs is not yet known. The best results thus far reported for the control of severe hypertensive states have been attributed to the combination of hexamethonium and hydralazine. Young patients with malignant hypertension and good renal function seem particularly sensitive to this combination. Insufficient clinical experience with pentamethylene pyrrolidinium bitartrate is available to indicate its exact place in therapy; preliminary observations have demonstrated it to be equally as effective as hexamethonium. Further trials of various drugs in combination are needed in order to clarify this extremely important problem.

Summary

Since primary arterial hypertension is a disease of complex etiology involving multiple factors, it seems entirely logical to attack the hypertensive process in as many ways as possible. Each patient must be treated as a whole, both mentally and physically, by using practical psychotherapy along with proper division of rest, relaxation and recreation. From the drug standpoint alone, the use of a combination of drugs with different pharmacologic actions seems ideal. At present no available drug or combination of drugs is a panacea for the hypertensive problem. Sodium restriction, although a controversial problem after years of investigation, appears to enhance the hypotensive effects of drug therapy and certainly seems indicated for patients who have significant tissue disease. Sympathectomy is reserved for younger patients with progressive hypertension who are unresponsive to intelligent medical management.

MEETINGS *and Postgraduate Courses*

UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER:
Sixth annual Colorado intern and resident clinics, June 2-3.
Colorado medical alumni clinics, June 10.
Fundamental advances in internal medicine, June 13-17.
Clinical hematology, July 11-15.
Dermatology for general practitioners, July 14-16.
Postgraduate seminar in ophthalmology, July 25-28.

AMERICAN MEDICAL WRITERS' ASSOCIATION: Twelfth annual meeting, September 30-October 1, at the Hotel Jefferson, St. Louis, with a workshop on medical writing, October 1.

AMERICAN INSTITUTE OF DENTAL MEDICINE: Twelfth annual meeting at the Desert Inn, Palm Springs, California, October 23-27. Applications and full information may be obtained from the Executive Secretary, Miss Marion G. Lewis, American Institute of Dental Medicine, 2240 Channing Way, Berkeley 4, California.

LOUISIANA STATE UNIVERSITY SCHOOL OF MEDICINE, NEW ORLEANS: Course in laboratory diagnosis and pathology of parasitic infections, August 15-27. Course is designed primarily for pathologists and technologists but is open to others. Additional information available from Dr. Clyde Swartzwelder, Department of Microbiology, Louisiana State University School of Medicine, New Orleans.

POSTGRADUATE CONTINUATION COURSE

Fitzsimons Army Hospital and
University of Colorado School of Medicine

I. Chronic Nontuberculous Pneumonia

H. WM. HARRIS*

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PRIOR to the era of effective antimicrobic therapy, lobar pneumonia in adults usually was caused by the *Pneumococcus*.[1] Although pneumococcic pneumonia is still common, it is rarely seen now in the classic lobar form. Characteristically, the inflammatory lesion of pneumococcic pneumonia undergoes complete resolution, and, in the absence of complicating factors such as bronchial occlusion, vascular occlusion, empyema, etc., permanent injury to lung tissue rarely occurs. Other types of pneumonia, however, pursue a chronic clinical course. They respond inadequately to the usual antibiotic therapy, and resolution either does not occur or is delayed. In fact, failure of pneumonia to respond promptly to antibiotic therapy indicated for pneumococcic infection may provide the first clinical evidence that chronic pneumonia exists. The purpose of this report is to review the etiologic and clinical aspects of nontuberculous chronic pneumonia and to provide a practical clinical approach to its diagnosis and treatment.

The proper management of chronic pneumonia requires an accurate etiologic and pathologic diagnosis. As the symptoms, physical signs and roentgenographic appearance of chronic pneumonia only rarely provide a specific etiologic diagnosis, it is of great importance for treatment purposes that the disease be properly classified into one of three broad categories:

1. Pulmonary infection in which chronicity results from the lung-destroying properties of the etiologic agent.

2. Pulmonary infection which is protracted because of abnormalities of the host.

3. Pulmonary infection in which resolution occurs but is delayed because of the host-parasite relationship, and in which destruction of lung tissue does not usually occur.

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Pneumonia Associated with Lung Destruction

Aspiration pneumonia—One of the most common causes of protracted pneumonia is pulmonary infection due to the aspiration of oral contents. This material gains entrance into the lung parenchyma by aspiration from the oropharynx. Aspiration occurs most often during states of unconsciousness or depressed consciousness when the gag, laryngeal and cough reflexes are depressed, as in alcoholic intoxication, surgical anesthesia, epileptic convulsions, diabetic coma or insulin reaction, head injury or deep sleep induced by sedation. Gastric contents, foreign bodies from the mouth, saliva and pharyngeal exudate may be aspirated during states of cerebral depression. In most instances, however, bacteria from the mouth also gain entrance to the lung by contamination of the aspirated material. How important the role of aspirated gastric juice and stomach contents is in the production of aspiration pneumonia in the human being is not entirely known.

In an experimental study on rabbits, Teabeaut[2] noted that the intratracheal instillation of acid solutions with a pH above 2.5 caused an acute, transitory inflammatory reaction and that instillation of solutions with a pH of 2.4 or less produced a chronic inflammatory reaction. He also found that gastric enzymes play little or no etiologic role in chronic inflammatory pulmonary reactions in animals. The nature of the lesion observed after intratracheal instillation of organic food substances depended on the size, shape and consistency of the particulate matter. Particles lodging in the bronchi or bronchioles produced obstruction with resulting chronic inflammation in the peripheral lung parenchyma. If obstruction was incomplete, the irritating effects of the foreign body frequently caused complete obstruction and chronic organizing pneumonia. It is probable that aspiration of both gastric contents and anaerobic bacteria are important factors in the etiology of aspiration pneumonia in the human being.

Amberson[3] noted a high incidence of pyorrhea alveolaris in patients with aspiration pneumonia, and observed few edentulous individuals with this disease. The anaerobic organisms present in gingival infections have been shown capable of producing putrid pneumonia and lung abscesses in the experimental animal.[4] The initial acute inflammation likely is due to the irritating effects of gastric juice acid and food particles. This process is associated with occlusion of the bronchi and bronchioles by the inflammatory reaction and particulate foreign material. The inflamed nonaereated, poorly drained pulmonary segment offers an ideal culture medium for the aspirated anaerobic bacteria. Invasion by these organisms in turn results in necrosis and suppuration of lung tissue.

Clinically, the infection is characterized by chills, fever, pleuritic pain, and, initially, by an unproductive cough. As necrosis develops, the patient begins to raise fetid purulent sputum. With excavation, the sputum becomes copious. It is important to note that some patients with aspiration pneumonia raise nonfetid sputum, and, even more commonly, when effective chemotherapeutic agents are given, the sputum rapidly loses its odor. Thus, foul sputum may not be demonstrated in aspiration pneumonia treated with penicillin before the etiologic diagnosis is established. In this instance a history of foul sputum prior to treatment may be obtained. Physical examination usually reveals dullness to percussion, rales and depressed breath sounds and voice sounds. These signs result from the bronchial occlusion produced by the inflammatory reaction and the necrotic exudate.

The roentgenogram usually demonstrates a homogenous density which often has a segmental distribution. Later in the disease, x-ray evidence of excavation may be apparent. The course of the illness may be rapid with destruction of large areas of lung tissue, overwhelming sepsis and death. With less extensive involvement, necrosis, excavation and fibrosis occur in a lobar, segmental or subsegmental distribution. Even with therapy, resolution may be slow and incomplete, and bronchiectasis, pulmonary fibrosis and residual lung abscesses may result. The boundary between suppurative pneumonia and lung ab-

scess is difficult to define. In most instances, necrotizing pneumonia develops first following aspiration. Later in the disease, particularly when treatment is delayed, sloughing and excavation may occur.

Staphylococcic pneumonia—The course of a pneumonia due to *Staphylococcus aureus* is variable.[5] Acute fulminating staphylococcic pneumonia is associated with widespread hemorrhagic necrotizing alveolitis, bronchitis and tracheitis, and may be fatal within 24 to 48 hours. The more chronic form of staphylococcic pneumonia is characterized by multiple lung abscesses in both the pulmonary parenchyma and the bronchial walls. The chronic inflammatory process is accompanied by an extensive fibrous reaction. This type of pneumonia may be protracted, and, even with intensive therapy, has a marked tendency to recur. As a result of the extensive interstitial fibrosis, cor pulmonale may develop in the end stages. An etiologic diagnosis can be established only by the demonstration of *Staph. aureus* in the sputum or blood.

Streptococcic pneumonia—Pulmonary infection due to *beta hemolytic streptococci* generally accompanies or follows an acute attack of streptococcic tonsillitis, or pharyngitis in adults, or may accompany the exanthematous diseases in children. Characteristically, this organism produces an acute interstitial pneumonitis with multiple small abscesses. Empyema is common. Even with effective treatment, resolution is slow, and residual bronchiectasis and fibrosis are common.

Friedländer's pneumonia—Pneumonia due to *Klebsiella pneumoniae* occurs chiefly in the older age groups and particularly in association with chronic alcoholism or general debility. The lung shows massive heavy consolidation with areas of necrosis filled with gelatinous exudate. The heavy exudate frequently produces bronchial occlusion, which favors further necrosis and excavation. The immediate mortality due to this disease has been reduced somewhat by antimicrobic therapy; however, destruction of lung parenchyma with residual bronchiectasis and lung abscess may occur in spite of effective treatment. The diagnosis can be established only by isolating the specific organism from the sputum or blood.

Pneumonia due to other bacteria—Chronic pneumonia associated with varying degrees of bronchial destruction and pulmonary fibrosis is seen occasionally in infections caused by other organisms. Among these are the various species of *Brucella*, and *Pasteurella tularensis*, *Diplococcus pneumoniae*, type III, *Hemophilus influenzae*, *H. pertussis*, *Streptococcus viridans* and *Staph. albus*. The gram-negative enteric bacilli *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus proteus* may, at times, cause similar chronic pulmonary infections. These organisms are most likely to invade the lungs during or immediately after a course of antimicrobic therapy for other diseases. The *Bacteroides* genus of gram-negative bacilli also has been isolated from chronic suppurative pneumonia, lung abscesses and empyema.[6]

Pneumonia due to fungi—Chronic pneumonia which may be associated with pulmonary excavation is sometimes caused by fungi. In this country, *Coccidioides immitis* and *Histoplasma capsulatum* are the most common etiologic agents. Less common causes are *Actinomyces*, *Cryptococcus* and *Nocardia*.

Pneumonia due to septic emboli—Protracted pneumonia which may go on to suppuration and abscess formation may occur as a complication of septic pulmonary emboli. The primary source of emboli is usually osteomyelitis, thrombophlebitis or pelvic infection.[7]

Chemical pneumonia—Various chemical agents may produce a chronic form of pneumonitis. Aspiration of gastric juice has been considered. Aspiration of small amounts of gastric or esophageal contents into the lung repeatedly over long periods of time may cause chronic organizing pneumonia associated with marked contraction and fibrous replacement of the parenchyma, rather than the acute suppurative pneumonia which accompanies the sudden aspiration of larger amounts of gastric contents. The chronic aspiration is produced usually by lesions of the esophagus or upper part of the gastrointestinal tract.

Pneumonia due to aspiration of mineral or vegetable oils is usually unresolving and of a chronic organizing nature. It is seldom sup-

purative. This disease is seen most often in debilitated persons who use mineral oil as a laxative habitually or in those who have practiced the frequent and prolonged use of oily nose drops. Various hypersensitivity states are occasionally associated with chronic or migratory pneumonitis. Chief among these are Löffler's syndrome and rheumatic pneumonia.

Chronic Pneumonia Associated with Primary Abnormalities of the Host

Impairment of lung ventilation and tracheobronchial cleansing favors the development of chronic organizing or suppurative pneumonia. Maintenance of normal ventilation and lung cleansing capacity is dependent on: (1) an unobstructed, physiologically active airway from the pharynx to the alveoli, (2) normal structure and function of the thoracic cage and the neuromuscular apparatus concerned with respiration and coughing, and (3) the normal elasticity of the lung. Primary abnormalities which favor the development of pneumonia can be classified as follows: (1) obstruction of the airway, (2) impairment of respiratory motion or of the cough reflex, and (3) impairment of pulmonary elasticity.

Obstruction of the airway may be anatomic or physiologic. Anatomic bronchial obstruction, in turn, may be classified as intrinsic or extrinsic. Intrinsic obstruction is due to such pathologic conditions as carcinoma, adenoma, foreign bodies, polyps, eroded lymph nodes, and granulomatous or fibrotic stenosis. Extrinsic obstruction may be caused by such conditions as enlarged lymph nodes, mediastinal tumors, and aortic aneurysms. Physiologic bronchial obstruction may be due to impaired ciliary action, alteration of bronchial contractility, and bronchospasm, any of which may be associated with bronchiectasis, bronchitis, bronchiolitis, asthma and pulmonary fibrosis.

Impairment of respiratory motion may be due to abnormalities of the thoracic cage or respiratory musculature. The abnormalities of the thoracic cage may result from thoracoplasty, fractures of the ribs, sternal excavation, severe kyphoscoliosis, pleural fibrosis and long-standing pleural effusion. Impairment of the respiratory musculature may be due to intercostal weakness or paralysis, or to diaphragmatic weakness or paralysis.

Depression of the cough reflex may be caused by coma, surgical anesthesia or depressant drugs. Impairment of pulmonary elasticity may be due to pulmonary emphysema or fibrosis.

The roentgenographic shadows observed in the lung parenchyma distal to an occluded bronchus are frequently termed "atelectasis." Pathologic examination of this area, however, reveals chronic organizing or suppurative pneumonitis and not simple "airlessness." McDonald, Harrington and Clagett[8] have analyzed the surgically excised lung tissue in 130 cases in which primary neoplasms involved the larger bronchi. In 98 cases, chronic "obstructive pneumonitis" was found in the lung parenchyma distal to the tumor. The various stages in the development of this pneumonia were investigated. Early, the obstructive lesion produced a damming back of secretions into the bronchi and alveoli; the bronchi were dilated and filled with mucus and serum. The involved portion of the lung was not contracted but rather was more voluminous than normal. Inflammatory cells and bacteria were found early in the process. Within a short time, organization of the exudate ensued, and extensive fibrosis eventually occurred. Abscesses occasionally were observed within the area of organizing and necrotizing pneumonitis, and, if rupture into the pleura occurred, bronchopleural fistula and empyema developed. Interestingly, instances of obstructive pneumonitis were observed in which an adequate anatomic airway was found; in these instances, physiologic block of the egress of secretions was believed to be due to replacement of ciliated columnar epithelium by carcinoma cells, or to splinting of the wall of the bronchus by the invading neoplasm.

Antimicrobic therapy may result in symptomatic improvement and x-ray evidence of resolution of the chronic pneumonia associated with bronchial occlusion. Thus, the presence of chronic segmental pneumonia must always be suspected to be associated with underlying bronchial disease. A favorable re-

sponse to chemotherapy does not exclude the possibility of this relationship.

A similar organizing and suppurative chronic pneumonia may occur when bronchial drainage is not anatomically obstructed but is impaired by structural and functional abnormality. These factors hinder the removal of secretions and exudate from the bronchi and pulmonary parenchyma, favor stagnation, and predispose to infection with the common organisms from the pharynx. In the normal lung, these organisms have only a low-grade pathogenicity and are swept out or destroyed by the physiologic defenses. The most common example of this type of chronic pneumonia is seen in bronchiectasis. Here, destruction of the myo-elastic layer of the bronchial wall prohibits the normal contraction of the bronchus during exhalation and particularly during cough. Also, there appears to be an increase in thick mucus secreted by the bronchial glands present in a bronchiectatic bronchus. Thus, impairment of the normal mechanisms for evacuating intrabronchial secretions and the accumulation of quantities of mucus provide a favorable site for invasion by bacteria of low-grade pathogenicity.

The chronic pneumonia which complicates bronchiectasis usually resolves slowly even with effective antimicrobic therapy, and organization, fibrosis and excavation of the lung may occur. Ineffective cough, as seen in diaphragmatic paralysis, disease of the thoracic cage or emphysema, also may lead to retained secretions and an organizing or suppurative pneumonia.

Pneumonia Associated with Delayed but Eventual Resolution

Various types of pneumonia caused by viruses and *rickettsiae* may undergo prompt resolution within a few days, but in other cases complete resolution may be delayed for many weeks. Slow resolution may be seen in primary atypical pneumonia, ornithosis, psittacosis, Q fever, varicella and other forms of virus and rickettsial infections. Usually, the lung remains undamaged after resolution is complete, but occasionally pulmonary fibrosis or bronchiectasis may occur.[9] Also, damage of the pulmonary tissue may be the result of superinvasion by bacteria which cause necrosis of lung tissue.

It is hazardous, however, to accept a diagnosis of virus pneumonia on the basis of delayed resolution alone. The early diagnosis and treatment of the more serious forms of chronic pneumonia, e.g., those associated with lung destruction or the result of bronchial occlusion, require an immediate awareness of the possible existence of these diseases by the physician. A patient with a slowly resolving or nonresolving pulmonary infiltrate must never be assumed to have virus pneumonia until the possibility that the chronic pneumonia is secondary to more serious underlying lung disease has been thoroughly investigated and ruled out.

Although chronic pneumonia usually can be etiologically related to the factors discussed, there are occasional reports of cases in which the cause is unknown. Waddell, Sniffen and Sweet[10] reported 10 cases in which idiopathic nonsuppurative interstitial pneumonitis was characterized by the deposit of high concentrations of cholesterol and cholesterol esters within the diseased lung parenchyma. Kershner and Adams[11] reported 10 cases of chronic "nonspecific" suppurative pneumonitis. Gleichman, Leder and Zahn[12] reported the following causes of delayed resolution in 52 cases of pneumonia:

Impaired bronchial drainage	22
Bacteriologic and chemical factors	16
Intrinsic complications of the pneumonic process	12
Undiagnosed	2

In addition, many other forms of lung disease are easily confused with chronic nontuberculous pneumonia. Chief among these is tuberculosis which must be considered a diagnostic possibility in every case in which roentgenographic examination of the thorax has disclosed an abnormality. Pulmonary emboli, vascular disease, chronic granulomas, metastatic tumors, congenital anomalies and many other disease states may closely resemble chronic pulmonary infection.

Diagnosis

The importance of a thorough and painstaking search for the underlying cause of chronic pneumonia cannot be overemphasized. This must include a complete history and physical examination, careful roentgenographic study, as well as laboratory investigation. Adequate bacteriologic and cytologic studies of sputum and bronchial secretions are important, and anaerobic cultures may add useful information. Bronchoscopy and bronchography are usually necessary. Finally, if a definite etiologic diagnosis cannot be established by clinical study, exploratory thoracotomy for diagnostic purposes is indicated. It is hazardous to assume a "watch and wait" attitude in a case of undiagnosed chronic pneumonia. The high incidence of lung cancer as the basic cause in these cases clearly justifies surgical intervention as a diagnostic procedure.

Treatment

The proper treatment for chronic pneumonia is selected on the basis of the etiologic factors responsible for the infection. Acute suppurative pneumonia due to aspiration requires the prompt use of two general types of therapy: (1) effective antimicrobic agents, and (2) measures designed to promote bronchial drainage. Penicillin is the drug of choice in most cases of aspiration pneumonia since the organisms associated with this disease are usually highly sensitive to this antibiotic. The minimal dose of penicillin which will effectively control the infection is not known, although it undoubtedly varies in individual cases. It is important to initiate therapy as early as possible in order to interrupt the rapid progression of lung destruction and to administer doses of penicillin which will provide a high concentration of this antibiotic in the blood. Most patients respond adequately to 600,000 units of penicillin G given intramuscularly every four hours during the early phases of the pneumonia.

Equally important is the necessity for bronchial drainage. Bronchoscopy should be performed early to investigate the possibility of a bronchial occluding lesion as well as to promote drainage. Sometimes, repeated bronchoscopy and tracheal aspiration are required to maintain drainage. The patient should be encouraged to cough, and cough-suppressant drugs should not be used. The patient should perform postural drainage at frequent intervals. The optimal position for this maneuver is that which provides the best gravity drainage of the infected lobe or segment. Observation of the patient during this exercise and repeated trials at various positions will allow selection of the most effective position. Postural drainage should be used every hour during the day and night.

With therapy, clinical improvement usually occurs within 24 to 48 hours. Fever subsides and the sputum may be noted to have a less offensive odor. With continuation of treatment, roentgenographic examination may show beginning resolution within several days. When the pneumonia is not extensive and treatment is begun early, improvement may continue until all symptoms subside and the chest roentgenogram appears normal. However, if the pneumonia is extensive and treatment is begun late, cough and expectoration may continue and resolution may be incomplete. Usually, the patient will have few symptoms by the time maximal resolution occurs, but if cough and purulent sputum continue, repeated use of Gram's stain and repeated cultures of the sputum are indicated since superinfection of the lung by a drug-resistant bacterial strain may have occurred. In this instance, in vitro tests for antimicrobic sensitivity of the predominating organism should be performed, and treatment should be altered accordingly.

After maximal resolution has occurred, regardless of whether the conventional roentgenogram appears normal or abnormal, every patient should be investigated for the presence of residual, irreparable damage of the lung. This is best carried out by laminagraphic studies of the lungs and by bronchography. It may be difficult to fill the bronchi of the pneumonic area, but, with proper positioning and selective instillation of the contrast medium under fluoroscopic control, this can usually be accomplished. With these technics, residual bronchiectasis or small lung abscesses may be

visualized. The indication for surgical resection of the residual bronchial or parenchymal lesions must be determined on the basis of clinical judgment in each case. The over-all surgical risk, considering the patient's age, general health and pulmonary function, must be evaluated and compared with the potential risk of morbidity and mortality expected from the residual pulmonary lesion.

Of equal importance is the prevention of subsequent attacks of aspiration pneumonia. A diligent effort should be made to prevent the episodes of coma which favor aspiration by patients who are subject to bouts of unconsciousness (diabetics, epileptics and alcoholics). Strict attention must be given to oral hygiene in these individuals. Total dental extraction with the substitution of dentures often is necessary to prevent pyorrhea.

Staphylococcic pneumonia requires intensive treatment with specific antibiotics. Since a large proportion of strains of *Staphylococcus* are resistant to penicillin, it is imperative that in vitro tests of sensitivity to various antibiotics be obtained as early as possible. The penicillin-resistant strains may respond to erythromycin or chloramphenicol, and in this case the therapeutic agent is best chosen on the basis of the degree of in vitro sensitivity. If the *Staphylococcus* recovered from sputum or blood is sensitive to penicillin, large doses of an aqueous solution of crystalline penicillin should be given intramuscularly at frequent intervals in order to provide a high concentration in the blood. Improvement of bronchial drainage is indicated to promote the evacuation of lung abscesses and areas of bronchial destruction. Therapy should be continued until there no longer is any clinical or roentgenographic evidence of activity of the infection. After discontinuance of treatment, the patient must be carefully observed for recurrent infection with *staphylococci.*

Group A *streptococci* are highly susceptible to the action of penicillin, and this is the antibiotic of choice in cases of streptococcic pneumonia. Pnuemonia due to *K. pneumoniae* does not respond to penicillin, but this organism is usually inhibited by streptomycin or drugs of the tetracycline series. It is important that intensive therapy with these agents be initiated early in cases of Friedländer's pneumonia since the acute infection carries a high risk of mortality. Surgical resection of a destroyed lobe or segment may be required after the acute infection has been controlled. Selection of the proper treatment for pneumonia caused by the gram-negative bacteria and for other less common types of bacterial pneumonia previously discussed must be based on the in vitro sensitivity of the different organisms to antibiotics.

The proper treatment for "obstructive pneumonia" distal to bronchial occlusion depends on the nature of the bronchial lesion. Usually, surgical extirpation of the diseased bronchus and parenchyma is indicated. However, once the bronchial occlusion is recognized, antibiotic therapy should be used to reduce the activity of the infection, to prevent serious complications such as bronchopleural fistulas and empyema, and to reduce the surgical risk. Penicillin is usually the drug of choice for this purpose.

Treatment of pneumonia complicating chronic primary lung disorders associated with impaired bronchial drainage necessitates special efforts to establish bronchial drainage. These measures are identical to those discussed previously. When the underlying lung disease is localized, as in bronchiectasis, fibrothorax, diaphragmatic paralysis, etc., bronchoscopic aspiration is indicated early, and this must be followed by effective and frequent postural drainage. When the pneumonia complicates widespread diffuse bronchial disease, as in pulmonary emphysema or asthma, not only are these measures indicated but also a bronchodilator drug (ISUPREL® hydrochloride or VAPONEFRIN®) should be used by nebulization. In many instances, drainage can be improved by nebulization of the bronchodilator drug during intermittent positive pressure breathing.

Antimicrobic therapy should be selected on the basis of the bacterial flora of the sputum and the effective inhibitory concentration of various antibiotics for the predominating organisms. Penicillin is usually the most effective agent in this type of chronic pneumonia.

The indication for surgical treatment in chronic pneumonia complicating primary, anatomic or physiologic abnormalities of the lung must be based on the nature of the underlying abnormality. Surgery may be indicated for localized chronic bronchial disease such as bronchiectasis, after the pneumonia has been controlled by medical therapy. In general, operation is not indicated for chronic pneumonia complicating diffuse pulmonary disease, such as pulmonary fibrosis or pulmonary emphysema, unless serious localized residual lesions result. Here, the risk of surgery must be weighed against the patient's reduced pulmonary function, and it is usually quite high.

Summary

Uncomplicated pneumococcic pneumonia usually resolves completely without residual lung damage. Chronic nontuberculous pneumonia is usually the result of the lung-destroying characteristics of the invading organism or agent, or the result of underlying chronic lung disease. Virus and rickettsial pneumonia may resolve slowly, but usually does not produce any residual lung damage. An unrelenting search for the responsible etiologic factors is of the utmost importance in proper management. When a definite etiologic diagnosis cannot be established, exploratory thoracotomy is indicated. Treatment should include specific antibiotic agents, the institution of bronchial drainage, and at times the surgical removal of bronchial disease or residual damaged lung tissue.

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II. Nontuberculous Empyema

During the past 10 years, the use of effective antimicrobic agents has markedly altered the treatment of pneumonia. Although the general incidence of pneumonia has been only slightly lowered by the extensive use of this therapy, the mortality rate has been reduced significantly.[1] The incidence of purulent complications also has been lowered, but, unfortunately, they still occur. Prior to the modern era of chemotherapy, the over-all incidence of purulent complications was reported to be 7.3 per cent, and, within recent years, this has been reduced to 4.3 per cent.[1] These complications continue to develop most often in patients with chronic debilitating diseases, or with chronic lung disease. Empyema may develop as a complication of pneumococcic pneumonia, and may accompany pulmonary infections caused by streptococci, staphylococci, Friedländer's bacilli and the mixed bacterial flora associated with putrid infections.

The use of antibiotics has been largely responsible for the reduction in morbidity and mortality rates in cases of empyema in recent years. Improvement in clinical results in the future can be achieved by careful attention to the fundamental principles of therapy and by close co-ordination of the medical and surgical aspects of management.

The classic symptoms of empyema—high

spikelike temperature, tachycardia, dyspnea and cyanosis—are not often seen at the present time since, in most instances, patients with pneumonia receive antibiotic therapy early in the disease. It is important to detect the presence of pleural infection before this complication is evidenced by increasing symptoms or by a suboptimal response to the treatment of the pneumonia. This is best achieved by frequent and careful physical examination of the chest with particular attention to signs of increasing dullness to percussion and suppression of tactile fremitus and the breath, voice and whispered sounds. Chest roentgenograms should be made frequently in both the postero-anterior and lateral projections. However, small amounts of pleural fluid often may be more readily detected by physical examination than by roentgenographic examination. The most important factor in detecting empyema is a constant awareness on the part of the physician that this complication may occur during pneumonia.

The presence of fluid in the pleural space during pneumonia is not evidence, per se, of empyema. Sterile pleural effusions have long been known to occur with pneumonia.[2] Prior to the advent of effective chemotherapy, most of these effusions gradually were resorbed. At present, however, sterile pleural effusions complicating pneumonia in patients receiving chemotherapy are difficult to evaluate, for it is often impossible to distinguish the originally sterile effusion from the small infected effusion which has been rendered sterile by chemotherapy. It is best, therefore, to confine the term empyema to a collection of pleural fluid which contains purulent exudate or from which bacteria can be recovered. The proper medical or surgical management of empyema includes: (1) control of the pleural infection, (2) establishment of pleural drainage, and (3) treatment of the underlying lung disease.

Treatment of Pleural Infection

The general principles of antibiotic therapy are applicable to the treatment of empyema. Effective treatment requires that the antibiotic should have an inhibitory effect on the invading organism and that it should be present in sufficient concentration to suppress bacterial growth. Penicillin is usually the drug of choice in cases in which the infection is due to gram-positive cocci (pneumococci, streptococci or staphylococci). Penicillin diffuses from the blood stream into the inflamed pleural cavity, and can be found in the pleural fluid in concentrations which are somewhat lower than those in the blood.[3] When penicillin is injected into the pleural cavity, it diffuses slowly into the blood stream, but considerable amounts remain in the pleural fluid from 24 to 72 hours after injection, depending on the dose used and the physical characteristics of the pleural cavity. Streptomycin has similar diffusion characteristics. In general, drugs of the tetracycline series cause considerable pleural irritation when injected into the pleural cavity.

It is of prime importance to establish the bacterial origin of the empyema. This is accomplished by thoracentesis and investigation of the bacterial content of the pleural fluid. Examination of the centrifuged sediment of pleural fluid with Gram's stain is an effective method for identifying the general type of bacteria, and it will provide sufficient information to permit one to start treatment. The organism should be identified by cultural methods. It is noteworthy that bacterial growth may not be obtained on culture if the patient is receiving or has received previous antimicrobic therapy, but organisms often can be demonstrated with Gram's stain for several days after treatment has been initiated.

Cultures should be obtained on routine media as well as on anaerobic media. Anaerobic cultures are chiefly of importance in detecting the mixed flora in cases of putrid empyema. Occasionally, Gram's stain and cultures of the purulent fluid will not reveal the etiologic organism in cases in which antibiotics have been administered. Selection of the proper drug in this instance must be made by demonstration of the etiologic organism in blood or sputum, or by a throat culture. In this instance, the possible presence of tuberculous empyema must be considered.

After the initial thoracentesis and identification of the organism, the proper antimi-

crobic agent should be injected into the pleural space. Penicillin is highly effective in cases in which empyema is due to pneumococci or streptococci, and in cases of putrid infection.[4] The usual intrapleural dose is from 100,000 to 200,000 units of crystalline penicillin diluted with physiologic saline solution. This dose should be administered at intervals of 24 to 48 hours, depending on the acuteness of the disease and the rapidity with which fluid reaccumulates. Penicillin also should be given intramuscularly to control the underlying pulmonary infection and to increase the concentration of drug in the pleural space.

Although penicillin remains the drug of choice in the treatment of staphylococcal empyema, the prevalence of penicillin-resistant strains of staphylococci requires that the sensitivity of the organism to various antimicrobic agents be determined as early as possible. If the strain proves resistant to penicillin, streptomycin or bacitracin may be used intrapleurally; if the organism is resistant to these agents, one of the tetracycline drugs must be used. *Klebsiella pneumoniae, Hemophilus influenzae* and the coliform bacilli usually are sensitive to streptomycin or to the tetracycline drugs. In cases in which empyema is due to one of these organisms, the drug should be selected after the sensitivity of the organism has been determined by in vitro tests. Both systemic and intrapleural routes of administration should be used. In general, intrapleural injection of the antibiotic should be continued until fluid can no longer be obtained by thoracentesis. Systemic therapy should be continued until resolution of the parenchymal lesions is well advanced and the pleural pocket is minimal. If surgical drainage is required, systemic therapy should be continued until the tubes are removed and all drainage has subsided.

Pleural Drainage

Drainage of purulent exudate continues to be of great importance in spite of the existence of effective measures for controlling bacterial growth. This principle is particularly applicable to pleural infections, for fibrinous exudates and large purulent clots are not resorbed from the pleural cavity. If they are not evacuated, they undergo fibrous organization, with the eventual development of extensive pleural fibrosis and the inevitable sequelae of recurrent bronchopulmonary infection, pulmonary fibrosis and impairment of pulmonary function.

The successful medical management of empyema requires that drainage of the pleural exudate be achieved. This can be done in most cases by repeated thoracentesis. The empyema pocket should be localized as accurately as possible by physical examination, chest roentgenograms and, particularly, by fluoroscopy. Thoracentesis should be performed with a large-caliber needle which must be introduced at various sites in order to evacuate the pleural space completely. On each occasion, withdrawal must be continued as long as fluid can be obtained. If the needle becomes obstructed with clots, irrigation of the needle and pleural cavity with sterile physiologic saline solution is required.

When the physical characteristics of the exudate prohibit adequate needle drainage, fibrinolytic agents should be introduced. Usually, a combination of streptokinase (250,000 units) and streptodornase (125,000 units) is instilled into the pleural space. Increased pleuritic pain and fever occur commonly within several hours after the instillation. Thoracentesis should be repeated within 6 to 12 hours to remove the reaccumulated pleural fluid. Crystalline trypsin (250 to 500 mg.) may be used as the fibrinolytic agent. The interval between instillations of the enzyme and the total dose given must be determined by requirements in the individual case. It is not advisable to use these agents until the pleural infection is well controlled.

Pleural drainage by thoracentesis followed by instillation of the antibiotic must be repeated at intervals of 12 to 24 hours in most cases. The usual cause of failure of the medical management of empyema is inadequate and incomplete removal of pleural exudate which results from long delayed or infrequent thoracenteses. If the exudate is not removed adequately in the early stage of the disease, it becomes thickened or solidified, and evacua-

tion by needle drainage becomes impossible. The only effective means of removal then is surgical decortication. Usually, there is a rapid subsidence of symptoms when thoracentesis is performed frequently and effective antimicrobic therapy instituted. The pleural fluid becomes thinner and less purulent; the volume gradually diminishes, and, finally, no fluid is obtained by thoracentesis. Chest roentgenograms often show a mild residual pleural reaction at this stage. The patient should then be instructed to perform breathing exercises by voluntarily elevating the affected hemithorax through a full range of inspiratory and expiratory motion for 5 to 10 minutes every hour during the day.

Putrid empyema due to a ruptured lung abscess, bronchopleural fistula or suppurative pneumonia has, in the past, represented a surgical emergency. However, early administration of penicillin by the intramuscular and intrapleural routes and adequate needle drainage usually control the toxemia promptly. Pleurocutaneous fistulas seldom, if ever, occur in cases in which this treatment is used. The pus rapidly loses its foul odor and becomes thinner. In many cases of putrid empyema, the patients have been cured with medical therapy alone.[4,5] Small bronchopleural fistulas have been present in some cases.

Control of Pulmonary Infection

The medical management of pneumonia, pulmonary suppuration, bronchiectasis and other lung diseases which result in empyema is beyond the scope of this paper. The basic principles of the medical treatment of the underlying lung disease are not significantly altered by the presence of empyema, and treatment should be carried out concomitantly with that for the empyema. It is important that the underlying lung be thoroughly evaluated after the empyema is successfully treated. Often, the presence of underlying bronchiectasis or lung abscess is detected only by laminagraphy, bronchoscopy or bronchography.

Co-ordination of Medical and Surgical Therapy

The indications for early surgical drainage in cases of nontuberculous empyema are: (1) the inability to evacuate the empyema cavity by thoracentesis, (2) the presence of organisms which are not sensitive to antibiotics, (3) the presence of large bronchopleural fistulas, (4) the persistence of bacteria in the pleural fluid in spite of intensive medical therapy, and (5) the presence of a large volume of empyema fluid with severe embarrassment of respiration. (This situation is most often encountered in children.) However, even in cases of empyema in which the patients are not completely cured by medical therapy, the pleural infection will become localized and marked clinical improvement will occur. Medical management will, therefore, allow elective surgical therapy in the form of surgical decortication and total extirpation of the infected pleural sac. Indications for surgical decortication in cases of empyema are significant fibrinous residua, persistent localized pockets of empyema fluid, chronic prolonged empyema, chronic draining sinuses, and a persistent thick and rigid pleura. Experience up to 1946 indicated that more than half of all patients with nontuberculous empyema could be cured by medical therapy.[4] At the present time, emergency thoracotomy is rarely indicated except for empyema associated with a large bronchopleural fistula. The majority of patients can be treated successfully by careful medical management. Even in those cases in which the patients are not cured by medical therapy, the infection is controlled and localized sufficiently to allow performance of elective surgical procedures at a considerably lowered risk.

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Editorials

Postgraduate Medicine

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"SPECIFIC ALARM SYNDROMES"?

EVER since the description in 1936 of "A syndrome produced by diverse nocuous agents,"[1] there has been much debate about the degree of nonspecificity of this "general adaptation syndrome" or standard "stress-response," as it is now called. Some authors believed that too many specific physiologic reactions and disease entities are, somewhat artificially, forced into the frame of the adaptation syndrome and particularly its first stage, the alarm reaction. This it was felt weakens the concept because, through such extensions, the stereotyped standard stress-response gradually tends to lose its meaning. Conversely, others—whose opinions have been excellently summarized in a recent editorial in POSTGRADUATE MEDICINE[2]—are reluctant to accept "the hypothesis of the completely nonspecific nature of this response." Similarly a reviewer of the psychiatric implications of the general adaptation syndrome concluded that "one has to distinguish between *specific* and *unspecific* stresses."[3]

These problems have been discussed at some length—with respect to the theoretical basis and practical applications of the stress-concept—in two monographs[4,5] and in the Annual Reports on Stress.[6] Because of the ever-increasing volume of research in this field it may be timely, however, to restate a few of the fundamental considerations which induced us to define the stress-syndrome as a nonspecific entity.

First, it is important to remember that, according to the original formulation of the stress-concept, all agents which act on the body or any of its parts exert dual effects: (1) *specific actions*, with which we are not directly concerned in stress-research and (2) *nonspecific or stressor effects* which may be direct or relayed (for instance, through the pituitary-adrenocortical axis or through the nervous system). The stressor action itself is viewed as causing an entirely nonspecific condition of stress.

At this point we must naturally ask: What is stress? For practical purposes we defined it as "a nonspecific deviation from the normal resting state, due to function or damage." From a slightly different point of view, it has also been described as "the sum of the nonspecific biologic phenomena, including damage and defense."[5]

It is difficult to give a more fundamental definition of stress, but this does not detract much from the utility of this concept. It

would be equally difficult—if not impossible—to define "Life," and yet, physiology and pathology could hardly have developed without this notion.

In any event, it will be observed that, in formulating our concept, biologic stress was designated as nonspecific by definition. We attach great importance to this. In our opinion, it was not any lack of materials (instruments, chemicals) but the purely mental handicap of not appreciating the indispensability of this formulation that was principally responsible for the failure to develop the stress-concept in medicine centuries ago.

Walter B. Cannon's work on "homeostatic mechanisms" probably came closest to it, except for the principle of nonspecificity. It is well to realize, therefore, how far-reaching the consequences of this difference can be. The specific "homeostatic reaction" to oxygen lack, for example, is quite distinct from that with which the body meets exposure to cold; the latter in turn is almost diametrically the opposite of that required to resist heat. These and many other highly specialized adjustments (e.g., serologic reactions to microbes, the hypertrophy of a muscle group in response to frequent use) are very important in the maintenance of what Claude Bernard called the "steadiness of the internal milieu," and which Cannon designated as "homeostasis." It must be kept in mind, however, that they represent precisely that part of the over-all response to various agents which we have to subtract in order to arrive at our "stress-syndrome," with its highly nonspecific corollaries, such as the discharge of ACTH, the secretion of corticoids, and the pathogenesis or treatment of inflammatory diseases.

Of course, our definition makes stress an abstraction, a factor which must be recognized and differentiated from the specific changes in every biologic reaction, although this separation can be accomplished only mentally and not materially. When a stressor acts on the body, the resulting condition of stress is necessarily always complicated by changes specific and typical of the eliciting agent (e.g., insulin causes hypoglycemia, pyrogens cause fever). A pure stressor does not actually exist in Nature; stressor potency is invariably attached to an agent which also possesses its own specific effects. However, Life is also an abstraction, which does not exist except in association with a living organism—a man, a microbe, a plant—whose specific features are not necessarily characteristic of Life as such.

Perhaps I could clarify my point with an analogy taken from chemistry. There is no substance which possesses only the properties of an acid, and hence we cannot study acidity except in association with the confusing specific characteristics of a compound which is acid. Phosphoric, sulfuric and acetic acid all possess specific chemical properties of their own, which clearly distinguish them from each other. Yet the abstract concept of acidity as such is quite indispensable. There are various acids, as there are various stressors, but there is only one acidity, as there is only one stress. It must merely be appreciated that the property of acidity (as the stressor potency) is invariably and inseparably attached to agents which, at the same time, possess quite unrelated specific effects of their own.

Since this is perhaps the most fundamental tenet of the stress-concept, it may be well to illustrate it with yet another analogy, this time taken from physics.

An electric current can produce the most diverse phenomena, but this does not imply that each manifestation requires a specifically different kind of electricity. By pressing one button or another in my car, I can produce motion (ignition), light (electric bulb), sound (radio, telephone), heat or cold (air-conditioning system); all of these are quite distinct "highly specific" effects and yet, they depend on the same kind of electric current.*

As Arnold[2] said in his editorial, "Stressor agents are capable of exerting some specific effects on man in addition to the nonspecific activation of the pituitary-adrenocortical axis."

*In the interest of scientific accuracy, I wish to state clearly that this part of the discussion is based purely on a theoretical generalization, not on objective observation. Actually, most of these gadgets do not function or have never been installed in my 1941 model, but, in this instance again, we do not feel that the necessity of abstract thinking diminishes the convincing force of our argument.

It is important to keep in mind, however, that these specific effects are merely attached to, and not identical with, the stressor actions of individual agents, although they may influence ("conditioning" or "permissive" effects) the latter. In this respect they are quite comparable with the phosphate and chloride reactions of phosphoric and hydrochloric acids which are inseparably attached to these chemical compounds, but not identical with their acid reactions.

If we are to analyze the physiology and pathology of nonspecific stress by objective scientific means it will be indispensable first to recognize and to define the limits of our subject.

HANS SELYE

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A SECOND LOOK AT CANCER

Elsewhere in this issue (page 280) Dr. George Crile, Jr., considers philosophically the surgical approach to cancer, emphasizing that "each cancer is a separate problem." In brief sentences the distinction between localized cancers that can be completely removed surgically and the rapidly metastasizing cancers that are disseminated by superradical surgery is made clear. "Patients submitting to radical operations for hopeless cancer suffer not so much from the cancers as from misguided attempts to control them." In his consideration of this delicate and debatable subject, Dr. Crile supports his point of view by statistical evidence. Today leaders emphatically urge early diagnosis and early operation as a sort of routine, standardized technic for assistance in the cancer problem. Other voices have supported the view that not even all patients with cancer of the breast are benefited by this attitude.

Dr. Crile is convinced that "the technics of radical cancer surgery have been carried far into the zone of diminishing returns." Thus his voice is a cry for conservatism and common sense in cancer, and this view is based on an honest recognition of our lack of knowledge or of certainty in distinguishing inoperable cancers from those that are operable. His forthright and independent statement will help to renew public confidence in surgical ethics.

MORRIS FISHBEIN

WIDOWS

The number of widows in the United States increased by 90 per cent during the years between 1920 and 1953, while the adult population of women gained only 63 per cent. In 1953 there were almost 7.5 million widows in the United States. At present one woman in every 10 in the age group from 45 to 54 is a widow, and the proportion is more than one in every four at ages 55 to 64.

The recent increase in widows is apparently chiefly in the cities. The statisticians who are responsible for these figures believe that many widows in rural areas who do not remarry soon move to the city.

The importance of these statistics lies in the fact that widows inherit considerable assets and thus have a considerable voice in the economic affairs of the country. The problem is important because of the large number of dependent children left in the care of widows, and the relationship between broken homes and delinquency is clearly established. Another question is the disproportion in life expectancy of the male population to that of the female population which is so significant as to demand special consideration.

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